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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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21 EXPEDIENTE No

04-51630

54 TITULO

DERIVADOS DE QUINAZOLINA COMO AGENTES ANTINEOPLASICOS

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71 SOLICITANTE

ASTRAZENECA AB

DOMICILIO

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74 APODERADO

RAMIRO CASTRO DUQUE

22 SANTAFE DE BOGOTA, D C

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1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☐ Capítulo I.		☒ Capítulo II.	
2 SOLICITANTE (71)	Nombre: ASTRAZENECA AB Dirección: S-151 85 Sodertälje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail:		IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:		IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 170.322 TP 1003
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10

ANEXOS

2

7

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$422.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE, RAMIRO CASTRO DUQUE

FIRMA:

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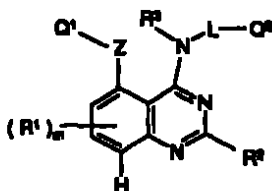
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WO 03/040109 A3

(54) Title: QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS



(57) Abstract: The invention concerns quinazoline derivatives of Formula (I); wherein each of Q¹, Q², Z, R¹, R², R³, L and m have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use in the prevention or treatment of tumours which are sensitive to inhibition of erbB receptor tyrosine kinases.

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QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS

The invention concerns certain novel quinazoline derivatives, or
5 pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are
accordingly useful in methods of treatment of the human or animal body. The invention also
concerns processes for the manufacture of said quinazoline derivatives, to pharmaceutical
compositions containing them and to their use in therapeutic methods, for example in the
manufacture of medicaments for use in the prevention or treatment of solid tumour disease in
10 a warm-blooded animal such as man.

Many of the current treatment regimes for diseases resulting from the abnormal
regulation of cellular proliferation such as psoriasis and cancer, utilise compounds that inhibit
DNA synthesis and cellular proliferation. To date, compounds used in such treatments are
generally toxic to cells however their enhanced effects on rapidly dividing cells such as
15 tumour cells can be beneficial. Alternative approaches to these cytotoxic anti-tumour agents
are currently being developed, for example selective inhibitors of cell signalling pathways.
These types of inhibitors are likely to have the potential to display an enhanced selectivity of
action against tumour cells and so are likely to reduce the probability of the therapy possessing
unwanted side effects.

20 Eukaryotic cells are continually responding to many diverse extracellular signals that
enable communication between cells within an organism. These signals regulate a wide
variety of physical responses in the cell including proliferation, differentiation, apoptosis and
motility. The extracellular signals take the form of a diverse variety of soluble factors
including growth factors as well as paracrine and endocrine factors. By binding to specific
25 transmembrane receptors, these ligands integrate the extracellular signal to the intracellular
signalling pathways, therefore transducing the signal across the plasma membrane and
allowing the individual cell to respond to its extracellular signals. Many of these signal
transduction processes utilise the reversible process of the phosphorylation of proteins that are
involved in the promotion of these diverse cellular responses. The phosphorylation status of
30 target proteins is regulated by specific kinases and phosphatases that are responsible for the
regulation of about one third of all proteins encoded by the mammalian genome. As
phosphorylation is such an important regulatory mechanism in the signal transduction process,
it is therefore not surprising that aberrations in these intracellular pathways result in abnormal

cell growth and differentiation and so promote cellular transformation (reviewed in Cohen *et al.*, Curr Opin Chem Biol. 1999, 3, 459-465).

It has been widely shown that a number of these tyrosine kinases are mutated to constitutively active forms and/or when over-expressed result in the transformation of a variety of human cells. These mutated and over-expressed forms of the kinase are present in a large proportion of human tumours (reviewed in Kolibaba *et al.*, Biochimica et Biophysica Acta, 1997, 133, F217-F248). As tyrosine kinases play fundamental roles in the proliferation and differentiation of a variety of tissues, much focus has centred on these enzymes in the development of novel anti-cancer therapies. This family of enzymes is divided into two groups - receptor and non-receptor tyrosine kinases e.g. EGF Receptors and the SRC family respectively. From the results of a large number of studies including the Human Genome Project, about 90 tyrosine kinase have been identified in the human genome, of this 58 are of the receptor type and 32 are of the non-receptor type. These can be compartmentalised in to 20 receptor tyrosine kinase and 10 non-receptor tyrosine kinase sub-families (Robinson *et al.*, Oncogene, 2000, 19, 5548-5557).

The receptor tyrosine kinases are of particular importance in the transmission of mitogenic signals that initiate cellular replication. These large glycoproteins, which span the plasma membrane of the cell possess an extracellular binding domain for their specific ligands (such as Epidermal Growth Factor (EGF) for the EGF Receptor). Binding of ligand results in the activation of the receptor's kinase enzymatic activity that is encoded by the intracellular portion of the receptor. This activity phosphorylates key tyrosine amino acids in target proteins, resulting in the transduction of proliferative signals across the plasma membrane of the cell.

It is known that the erbB family of receptor tyrosine kinases, which include EGFR, erbB2, erbB3 and erbB4, are frequently involved in driving the proliferation and survival of tumour cells (reviewed in Olayioye *et al.*, EMBO J., 2000, 19, 3159). One mechanism in which this can be accomplished is by overexpression of the receptor at the protein level, generally as a result of gene amplification. This has been observed in many common human cancers (reviewed in Klapper *et al.*, Adv. Cancer Res., 2000, 77, 25) such as breast cancer (Sainsbury *et al.*, Brit. J. Cancer, 1988, 58, 458; Guerin *et al.*, Oncogene Res., 1988, 3, 21; Slamon *et al.*, Science, 1989, 244, 707; Klijn *et al.*, Breast Cancer Res. Treat., 1994, 29, 73 and reviewed in Salomon *et al.*, Crit. Rev. Oncol. Hematol., 1995, 19, 183), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny *et al.*, Brit. J. Cancer, 1986, 54,

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265; Reubi *et al.*, Int. J. Cancer, 1990, 45, 269; Rusch *et al.*, Cancer Research, 1993, 53, 2379; Brabender *et al.*, Clin. Cancer Res., 2001, 7, 1850) as well as other cancers of the lung (Hendler *et al.*, Cancer Cells, 1989, 7, 347; Ohsaki *et al.*, Oncol. Rep., 2000, 7, 603), bladder cancer (Neal *et al.*, Lancet, 1985, 366; Chow *et al.*, Clin. Cancer Res., 2001, 7, 1957, Zhan *et al.*, Mol. Carcinog., 3, 254), oesophageal cancer (Mukaida *et al.*, Cancer, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen *et al.*, Oncogene Res., 1987, 1, 149; Kapitanovic *et al.*, Gastroenterology, 2000, 112, 1103; Ross *et al.*, Cancer Invest., 2001, 19, 554), cancer of the prostate (Visakorpi *et al.*, Histochem. J., 1992, 24, 481; Kumar *et al.*, 2000, 32, 73; Scher *et al.*, J. Natl. Cancer Inst., 2000, 92, 1866), leukaemia (Konaka *et al.*, Cell, 1984, 37, 1035, Martin-Subero *et al.*, Cancer Genet. Cytogenet., 2001, 127, 174), ovarian (Hallstrom *et al.*, Cancer Res., 2001, 61, 2420), head and neck (Shiga *et al.*, Head Neck, 2000, 22, 599) or pancreatic cancer (Ovotny *et al.*, Neoplasma, 2001, 48, 188). As more human tumour tissues are tested for expression of the erbB family of receptor tyrosine kinases it is expected that their widespread prevalence and importance will be further enhanced in the future.

As a consequence of the mis-regulation of one or more of these receptors (in particular erbB2), it is widely-believed that many tumours become clinically more aggressive and so correlate with a poorer prognosis for the patient (Brabender *et al.*, Clin. Cancer Res., 2001, 7, 1850; Ross *et al.*, Cancer Investigation, 2001, 19, 554, Yu *et al.*, Bioessays, 2000, 22, 7, 673). In addition to these clinical findings, a wealth of pre-clinical information suggests that the erbB family of receptor tyrosine kinases are involved in cellular transformation. This includes the observations that many tumour cell lines overexpress one or more of the erbB receptors and that EGFR or erbB2 when transfected into non-tumour cells have the ability to transform these cells. This tumourigenic potential has been further verified as transgenic mice that overexpress erbB2 spontaneously develop tumours in the mammary gland. In addition to this, a number of pre-clinical studies have demonstrated that anti-proliferative effects can be induced by knocking out one or more erbB activities by small molecule inhibitors, dominant negatives or inhibitory antibodies (reviewed in Mendelsohn *et al.*, Oncogene, 2000, 19, 6550). Thus it has been recognised that inhibitors of these receptor tyrosine kinases should be of value as a selective inhibitor of the proliferation of mammalian cancer cells (Yaish *et al.*, Science, 1988, 242, 933, Kolibaba *et al.*, Biochimica et Biophysica Acta, 1997, 133, F217-F248; Al-Obeidi *et al.*, 2000, Oncogene, 19, 5690-5701; Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565). In addition to this pre-clinical data, findings using inhibitory

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antibodies against EGFR and erbB2 (c-225 and trastuzumab respectively) have proven to be beneficial in the clinic for the treatment of selected solid tumours (reviewed in Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565).

Amplification and/or activity of members of the ErbB type receptor tyrosine kinases have been detected and so have been implicated to play a role in a number of non-malignant proliferative disorders such as psoriasis (Ben-Bassat, Curr. Pharm. Des., 2000, 6, 933; Elder *et al.*, Science, 1989, 243, 811), benign prostatic hyperplasia (BPH) (Kumar *et al.*, Int. Urol. Nephrol., 2000, 32, 73), atherosclerosis and restenosis (Bokemeyer *et al.*, Kidney Int., 2000, 58, 549). It is therefore expected that inhibitors of erbB type receptor tyrosine kinases will be useful in the treatment of these and other non-malignant disorders of excessive cellular proliferation.

International Patent Applications WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980 and WO 96/33981 disclose that certain quinazoline derivatives which bear an anilino substituent at the 4-position possess receptor tyrosine kinase inhibitory activity.

A review of the structure activity relationship of various quinazoline derivatives is disclosed by G. W. Rewcastle *et al.* (J. Med. Chem. 1995, 38, 3428-3487), including a number of 5-substituted compounds. However, such 5-substituted compounds are stated to have low in-vitro activity as EGFR tyrosine kinase inhibitors compared to quinazolines substituted at the 6- and 7- positions.

WO 96/09294 discloses 4-anilinoquinazoline derivatives, including 5-chloro and 5-methoxy substituted quinazoline derivatives as protein tyrosine kinase inhibitors.

Co-pending International Patent Application PCT/GB01/02424 discloses that certain quinazoline derivatives which carry a 5-substituent are inhibitors of the Src family of non-receptor tyrosine kinases, such as c-Src, c-Yes and c-Fyn.

We have now found that surprisingly certain 5-substituted quinazoline derivatives possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of one or more of the erbB family of receptor tyrosine kinases that are involved in the signal transduction steps which lead to the proliferation of tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-tumour effect by way of inhibition of EGFR and/or erbB2 receptor tyrosine kinases.

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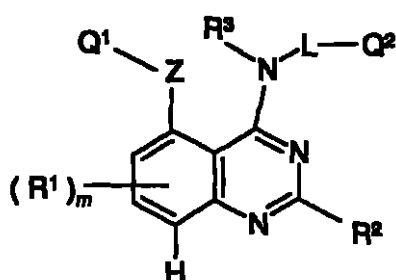
- 5 -

Generally the compounds of the present invention possess potent inhibitory activity against the erbB receptor tyrosine kinase family, for example by inhibition of EGFR and/or erbB2 and/or erbB4 receptor tyrosine kinases, whilst possessing less potent inhibitory activity against other kinases. Furthermore, certain compounds of the present invention possess

5 substantially better potency against the erbB2 over that of the EGFR tyrosine kinase, thus potentially providing effective treatment for erbB2 driven tumours. Additionally, certain of the compounds according to the present invention possess substantially better potency against the EGFR over that of the erbB2 tyrosine kinase. The invention also includes compounds that are active against all or a combination of EGFR, erbB2 and erbB4 receptor tyrosine kinases,

10 thus potentially providing treatments for conditions mediated by one or more of these receptor tyrosine kinases.

According to a first aspect of the invention there is provided a quinazoline derivative of the Formula I



15

wherein m is 0, 1 or 2;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy,

20 (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino,

25 N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



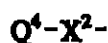
X 10

- 6 -

wherein X^1 is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein each R⁴ is, independently, hydrogen or (1-6C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl,
 5 (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_n is (1-3C)alkylenedioxy,

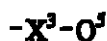
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein
 10 R⁵ is hydrogen or (1-6C)alkyl,

and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or
 15 from a group of the formula :



wherein X² is a direct bond or is selected from CO and N(R⁶)CO, wherein R⁶ is hydrogen or (1-6C)alkyl, and Q⁴ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,
 20 (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl- (2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



30 wherein X³ is a direct bond or is selected from O, S, SO, SO₂, N(R⁷), CO, CH(OR⁷), CON(R⁷), N(R⁷)CO, SO₂N(R⁷), N(R⁷)SO₂, C(R⁷)₂O, C(R⁷)₂S and N(R⁷)C(R⁷)₂, wherein R⁷ is hydrogen or (1-6C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-

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(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from
 5 halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkanoyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
 10 N-(1-6C)alkyl-(2-6C)alkanoylamino, amino(2-6C)alkanoyl, N-(1-6C)alkylamino(2-6C)alkanoyl, N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula:



15 wherein X⁴ is a direct bond or is selected from O and N(R⁹), wherein R⁹ is hydrogen or (1-6C)alkyl, and R⁸ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
 20 carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,
 or from a group of the formula :



25 wherein X⁵ is a direct bond or is selected from O, CO and N(R¹⁰), wherein R¹⁰ is hydrogen or (1-6C)alkyl, and Q⁶ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

30 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo or thioxo substituents;

R² is hydrogen;

R³ is hydrogen or (1-6C)alkyl;

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Z is a direct bond or is selected from O, S, SO, SO₂, N(R¹¹), CO, CH(OR¹¹), CON(R¹¹), N(R¹¹)CO, SO₂N(R¹¹), N(R¹¹)SO₂, OC(R¹¹)₂, SC(R¹¹)₂ and N(R¹¹)C(R¹¹)₂, wherein each R¹¹ is, independently, hydrogen or (1-6C)alkyl;

Q¹ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl,
5 (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q¹-Z- group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹²), CO, CH(OR¹²), CON(R¹²), N(R¹²)CO, SO₂N(R¹²), N(R¹²)SO₂, CH=CH and
10 C=C wherein R¹² is hydrogen or (1-6C)alkyl,

and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,
15 (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

20 $-X^7-Q^8$

wherein X⁷ is a direct bond or is selected from O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S and N(R¹⁴)C(R¹⁴)₂, wherein R¹⁴ is hydrogen or (1-6C)alkyl, and Q⁸ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl,
25 heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within the Q¹-Z- group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenylloxy,
30 (2-6C)alkynylloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,

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N-(1-6C)alkyl-(2-6C)alkanoylamino, amino(2-6C)alkanoyl,

N-(1-6C)alkylamino(2-6C)alkanoyl, N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl,

N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and

N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^8 is a direct bond or is selected from O and N(R^{16}), wherein R^{16} is hydrogen or (1-6C)alkyl, and R^{15} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,

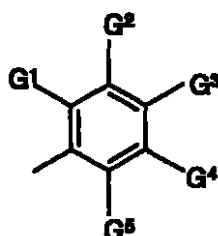
- 10 N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl, or from a group of the formula:



- wherein X^9 is a direct bond or is selected from O, CO and N(R^{17}), wherein R^{17} is hydrogen or (1-6C)alkyl, and Q^9 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q^1-Z group optionally bears 1 or 2 oxo or thioxo substituents;

- 20 Q^3 is an aryl group of formula Ia



Ia

wherein G^1 and G^5 are hydrogen,

- G^2 and G^4 each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, aryl and heteroaryl,

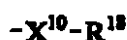
and wherein an aryl or heteroaryl group within any of G^2 and G^4 optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl,

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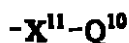
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cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

- G^3 is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- 15 wherein X^{10} is a direct bond or is selected from O and N(R^{19}), wherein R^{19} is hydrogen or (1-6C)alkyl, and R^{18} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



- 20 wherein X^{11} is a direct bond or is selected from O, S, SO, SO₂, N(R^{20}), CO, CH(OR²⁰), CON(R^{20}), N(R^{20})CO, SO₂N(R^{20}), N(R^{20})SO₂, C(R^{20})₂O, C(R^{20})₂S, C(R^{20})₂N(R^{20}) and N(R^{20})C(R^{20})₂, wherein R^{20} is hydrogen or (1-6C)alkyl, and Q^{10} is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- 25 and wherein Q^{10} optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, formyl, carbamoyl, sulphamoyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino,

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N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^{13} is a direct bond or is selected from O and $N(R^{24})$, wherein R^{24} is hydrogen or
 5 (1-6C)alkyl, and R^{23} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,
N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl,
 (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

10 and wherein any heterocyclyl group within Q^{10} optionally bears 1 or 2 oxo or thioxo substituents,

or G^3 and G^4 together form a group of formula :- $-CH=CH-CH=CH-$,

$-N=CH-CH=CH-$, $-CH=N-CH=CH-$, $-CH=CH-N=CH-$, $-CH=CH-CH=N-$, $-N=CH-N=CH-$,
 $-CH=N-CH=N-$, $-N=CH-CH=N-$, $-N=N-CH=CH-$, $-CH=CH-N=N-$, $-CH=CH-O-$,
 15 $-O-CH=CH-$, $-CH=CH-S-$, $-S-CH=CH-$, $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-CH_2-CH_2-S-$,
 $-S-CH_2-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-S-CH_2-S-$, $-S-CH_2-CH_2-S-$, $-CH=CH-NH-$,
 $-NH-CH=CH-$, $-CH_2-CH_2-NH-$, $-NH-CH_2-CH_2-$, $-N=CH-NH-$, $-NH-CH=N-$, $-NH-CH_2-NH-$,
 $-O-CH=N-$, $-N=CH-O-$, $-S-CH=N-$, $-N=CH-S-$, $-O-CH_2-NH-$, $-NH-CH_2-O-$, $-S-CH_2-NH-$,
 $-NH-CH_2-S-$, $-O-N=CH-$, $-CH=N-O-$, $-S-N=CH-$, $-CH=N-S-$, $-O-NH-CH_2-$, $-CH_2-NH-O-$,
 20 $-S-NH-CH_2-$, $-CH_2-NH-S-$, $-NH-N=CH-$, $-CH=N-NH-$, $-NH-NH-CH_2-$, $-CH_2-NH-NH-$,
 $-N=N-NH-$ or $-NH-N=N-$,

and the 9- or 10-membered bicyclic heteroaryl or heterocyclic ring formed when G^3
 and G^4 together are linked optionally bears on the heteroaryl or heterocyclic portion of the
 bicyclic ring 1, 2 or 3 substituents, which may be the same or different, selected from
 25 halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl,
 (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino and a group of the
 formula:



wherein X^{12} is a direct bond or is selected from O, SO, SO_2 , $N(R^{21})$, $SO_2N(R^{21})$ and CO,
 30 wherein R^{21} is hydrogen or (1-6C)alkyl and Q^{11} is aryl, aryl-(1-6C)alkyl, heteroaryl,
 heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2
 substituents, which may be the same or different, selected from halogeno, trifluoromethyl,
 cyano, nitro, hydroxy, amino, carboxy, formyl, carbamoyl, sulphamoyl, mercapto, (1-6C)alkyl,

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(2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy,
 (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,
 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,
N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
 5 N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl,
N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



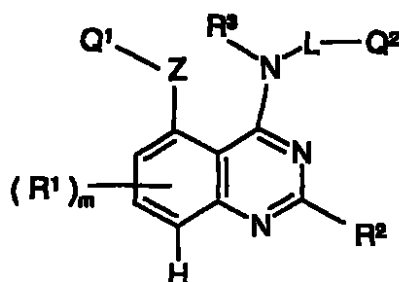
wherein X^{14} is a direct bond or is selected from O and N(R^{26}), wherein R^{26} is hydrogen or
 10 (1-6C)alkyl, and R^{25} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
 cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl,
 di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,
N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl,
 (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl; and

15 L is a direct bond or $-[C(R^{22})_n]_a-$, wherein n is 1 or 2, and each R^{22} independently is
 hydrogen or (1-4C)alkyl,

and when L is a direct bond at least one of G^2 , G^3 and G^4 is other than H;

or a pharmaceutically-acceptable salt thereof.

According to a further aspect of the present invention there is provided a quinazoline
 20 derivative of the formula I



25 wherein m is 0, 1 or 2;

each R^1 group, which may be the same or different, is selected from halogeno,
 trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy,

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carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- 10 wherein X^1 is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein each R⁴ is, independently, hydrogen or (1-6C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or
- 15 heterocyclyl-(1-6C)alkyl, or (R¹)_m is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl,

- 20 and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

- 25 $Q^4 - X^2 -$

wherein X^2 is a direct bond or is selected from CO and N(R⁶)CO, wherein R⁶ is hydrogen or (1-6C)alkyl, and Q⁴ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
- 30 said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

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(1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a

5 group of the formula :



wherein X^3 is a direct bond or is selected from O, S, SO, SO₂, N(R⁷), CO, CH(OR⁷), CON(R⁷), N(R⁷)CO, SO₂N(R⁷), N(R⁷)SO₂, C(R⁷)₂O, C(R⁷)₂S and N(R⁷)C(R⁷)₂, wherein R⁷ is hydrogen or (1-6C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-

10 (1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl,

15 (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl,

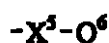
20 N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



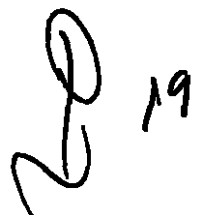
wherein X^4 is a direct bond or is selected from O and N(R⁸), wherein R⁸ is hydrogen or (1-6C)alkyl, and R⁸ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,

25 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl,

or from a group of the formula :



30 wherein X^5 is a direct bond or is selected from O, CO and N(R¹⁰), wherein R¹⁰ is hydrogen or (1-6C)alkyl, and Q⁶ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,



and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

R^2 is hydrogen;

R^3 is hydrogen or (1-6C)alkyl;

5 Z is a direct bond or is selected from O, S, SO, SO₂, N(R^{11}), CO, CH(OR¹¹), CON(R^{11}), N(R^{11})CO, SO₂N(R^{11}), N(R^{11})SO₂, OC(R^{11})₂, SC(R^{11})₂ and N(R^{11})C(R^{11})₂, wherein each R^{11} is, independently, hydrogen or (1-6C)alkyl;

Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl,
10 heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q^1 -Z- group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R^{12}), CO, CH(OR¹²), CON(R^{12}), N(R^{12})CO, SO₂N(R^{12}), N(R^{12})SO₂, CH=CH and C=C wherein R^{12} is hydrogen or (1-6C)alkyl,

15 and wherein any CH₂=CH- or HC=C- group within the Q^1 -Z- group optionally bears at the terminal CH₂= or HC= position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

20 Q^7-X^6-

wherein X^6 is a direct bond or is selected from CO and N(R^{13})CO, wherein R^{13} is hydrogen or (1-6C)alkyl, and Q^7 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH₂ or CH₃ group within the Q^1 -Z- group optionally bears on each
25 said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-
30 (2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

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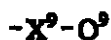
wherein X^7 is a direct bond or is selected from O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S and N(R¹⁴)C(R¹⁴)₂, wherein R¹⁴ is hydrogen or (1-6C)alkyl, and Q⁸ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl,

5 (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within the Q¹-Z- group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, 10 (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, 15 N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^8 is a direct bond or is selected from O and N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and R¹⁵ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, 20 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula:

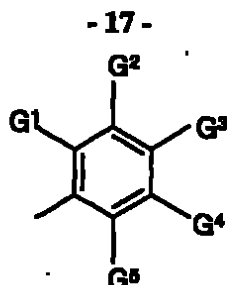


wherein X^9 is a direct bond or is selected from O, CO and N(R¹⁷), wherein R¹⁷ is hydrogen or (1-6C)alkyl, and Q⁹ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl 25 or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo or thioxo substituents;

Q² is an aryl group of formula Ia

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wherein G^1 and G^5 are hydrogen,

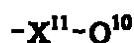
G^2 and G^4 each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, aryl and heteroaryl,

and wherein an aryl or heteroaryl group within any of G^2 and G^4 optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

G^3 is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^{10} is a direct bond or is selected from O and N(R^{19}), wherein R^{19} is hydrogen or (1-6C)alkyl, and R^{18} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



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wherein X^{11} is a direct bond or is selected from O, S, SO, SO₂, N(R²⁰), CO, CH(OR²⁰), CON(R²⁰), N(R²⁰)CO, SO₂N(R²⁰), N(R²⁰)SO₂, C(R²⁰)₂O, C(R²⁰)₂S and N(R²⁰)C(R²⁰)₂, wherein R²⁰ is hydrogen or (1-6C)alkyl, and Q¹⁰ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl,

5 heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein Q¹⁰ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl,

10 (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

15 and wherein any heterocyclyl group within Q¹⁰ optionally bears 1 or 2 oxo or thioxo substituents,

or G³ and G⁴ together form a group of formula :- -CH=CH-CH=CH-,

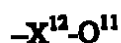
-N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-, -CH=N-CH=N-, -N=CH-CH=N-, -N=N-CH=CH-, -CH=CH-N=N-, -CH=CH-O-,

20 -O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH₂-CH₂-O-, -O-CH₂-CH₂-, -CH₂-CH₂-S-, -S-CH₂-CH₂-, -O-CH₂-O-, -O-CH₂-CH₂-O-, -S-CH₂-S-, -S-CH₂-CH₂-S-, -CH=CH-NH-, -NH-CH=CH-, -CH₂-CH₂-NH-, -NH-CH₂-CH₂-, -N=CH-NH-, -NH-CH=N-, -NH-CH₂-NH-, -O-CH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH₂-NH-, -NH-CH₂-O-, -S-CH₂-NH-, -NH-CH₂-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -CH=N-S-, -O-NH-CH₂-, -CH₂-NH-O-,

25 -S-NH-CH₂-, -CH₂-NH-S-, -NH-N=CH-, -CH=N-NH-, -NH-NH-CH₂-, -CH₂-NH-NH-, -N=N-NH- or -NH-N=N-,

and the 9- or 10-membered bicyclic heteroaryl or heterocyclic ring formed when G³ and G⁴ together are linked optionally bears on the heteroaryl or heterocyclic portion of the bicyclic ring 1, 2 or 3 substituents, which may be the same or different, selected from

30 halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula:





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wherein X^{12} is a direct bond or is selected from O, SO, SO₂, N(R²¹) and CO, wherein R²¹ is hydrogen or (1-6C)alkyl and Q¹¹ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy, and any

5 bicyclic heterocyclic ring so formed optionally bears 1 or 2 oxo or thioxo groups; and

L is a direct bond or $-[C(R^{22})_n]_n-$, wherein n is 1 or 2, and each R²² independently is hydrogen or (1-4C)alkyl,

and when L is a direct bond at least one of G², G³ and G⁴ is other than H;

or a pharmaceutically-acceptable salt thereof.

10 According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I wherein each of m, R¹, R², R³, L and Q² has any of the meanings defined hereinbefore and

Z is selected from O, S, SO, SO₂, N(R¹¹), CO, CH(OR¹¹), CON(R¹¹), N(R¹¹)CO, SO₂N(R¹¹), N(R¹¹)SO₂, OC(R¹¹)₂, SC(R¹¹)₂ and N(R¹¹)C(R¹¹)₂, wherein R¹¹ is hydrogen or

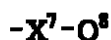
15 (1-6C)alkyl; and

Q¹ is selected from (3-7C)cycloalkyl, (3-7C)cycloalkenyl and heterocyclyl,

and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio,

20 (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a

25 group of the formula :



wherein X⁷ is a direct bond or is selected from O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S and N(R¹⁴)C(R¹⁴)₂, wherein R¹⁴ is hydrogen or (1-6C)alkyl, and Q⁸ is (3-7C)cycloalkyl,

30 (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- 20 -

- and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio,
- 5 (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, amino(2-6C)alkanoyl, N-(1-6C)alkylamino(2-6C)alkanoyl, N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl,
- 10 N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- wherein X⁸ is a direct bond or is selected from O and N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and R¹⁵ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
- 15 cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl, or from a group of the formula:



- wherein X⁹ is a direct bond or is selected from O, CO and N(R¹⁷), wherein R¹⁷ is hydrogen or (1-6C)alkyl, and Q⁹ is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

- 25 and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo or thioxo substituents.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I wherein each of m, R¹, R², R³, L and Q² has any of the meanings defined hereinbefore and

- 30 Z is selected from O, S, SO, SO₂, N(R¹¹), CO, CH(OR¹¹), CON(R¹¹), N(R¹¹)CO, SO₂N(R¹¹), N(R¹¹)SO₂, OC(R¹¹)₂, SC(R¹¹)₂ and N(R¹¹)C(R¹¹)₂, wherein R¹¹ is hydrogen or (1-6C)alkyl; and

25

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Q^1 is (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q^1 -Z- group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹²), CO, CH(OR¹²), CON(R¹²), N(R¹²)CO, SO₂N(R¹²), N(R¹²)SO₂, CH=CH and C≡C wherein R¹² is hydrogen or (1-6C)alkyl,

and wherein any CH₂ or CH₃ group within the Q^1 -Z- group optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, 10 (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a 15 group of the formula :



wherein X⁷ is a direct bond or is selected from O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S and N(R¹⁴)C(R¹⁴)₂, wherein R¹⁴ is hydrogen or (1-6C)alkyl, and Q⁸ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, 20 (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, 25 (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and 30 N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



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wherein X^8 is a direct bond or is selected from O and N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and R¹⁵ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X^9 is a direct bond or is selected from O, CO and N(R¹⁷), wherein R¹⁷ is hydrogen or (1-6C)alkyl, and Q^9 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

10 and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1 or 2 oxo or thioxo substituents.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I as hereinbefore defined wherein m is not 0 when:

Z is a direct bond or is selected from O, S and N(R¹¹), wherein R¹¹ is as hereinbefore defined;

15 and

(i) L is a direct bond, and Q^2 is an aryl group of the formula 1a as hereinbefore defined wherein G^3 is a group of the formula:



wherein X^{11} is a direct bond or is selected from O, S, SO, SO₂, N(R²⁰), CH(OR²⁰),
 20 CON(R²⁰), N(R²⁰)CO, SO₂N(R²⁰), N(R²⁰)SO₂, C(R²⁰)₂O, C(R²⁰)₂S, CO and C(R²⁰)₂N(R²⁰),
 wherein each R²⁰ is as hereinbefore defined, and Q^{10} is aryl, aryl(1-6C)alkyl, heteroaryl, or heteroaryl(1-6C)alkyl; or

(ii) L is a direct bond, and Q^2 is an aryl group of the formula 1a as hereinbefore defined wherein G^3 is $-X^{11}-Q^{10}$, wherein X^{11} is CO and Q^{10} is a nitrogen containing
 25 heterocyclyl group linked to X^{11} by a nitrogen atom; or

(iii) L is a direct bond, and Q^2 is an aryl group of the formula 1a as hereinbefore defined wherein G^3 and G^4 together form a group of the formula $-NH-CH=CH-$, $-CH=CH-NH-$, $-NH-N=CH-$ or $-CH=N-NH-$, which group is substituted at an NH group by a group of the formula:



wherein X^{12} is a direct bond or is selected from SO₂, CO, SO₂N(R²¹), wherein R²¹ is as hereinbefore defined and Q^{11} is aryl, aryl(1-6C)alkyl, heteroaryl, or heteroaryl(1-6C)alkyl.

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In this aspect of the invention it is preferred that when Z is a direct bond or is selected from O, S and N(R¹¹), wherein R¹¹ is as hereinbefore defined and any one of conditions (i), (ii) or (iii) defined above is satisfied, that m is 1 and R¹ is located at the 7-position, wherein R¹ is as hereinbefore defined.

5 In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and ~~tert~~-butyl, and (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are
10 specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy, cyclopropyloxy and cyclopentyloxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino and cyclohexylamino, and di-[(1-6Calkyl)]amino includes dimethylamino,
15 diethylamino, N-cyclobutyl-N-methylamino and N-cyclohexyl-N-ethylamino.

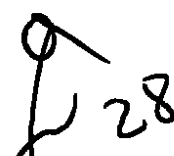
It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be
20 carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

It is to be understood that the present invention includes in its definition any and all
25 tautomeric forms of the compounds of the formula I which possess the above mentioned activity.

It is also to be understood that in so far as certain compounds of the formula 1 may exist in solvated forms as well as unsolvated forms, for example, hydrated forms, the present invention includes any and all such solvated forms, which possess the above mentioned
30 activity.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for any one of the 'Q' groups (Q¹, Q³ to Q¹¹), G² or G⁴ when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.



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A suitable value for any one of the 'Q' groups (Q^1 , Q^3 to Q^8 and Q^{10}) when it is (3-7C)cycloalkyl or for the (3-7C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups (Q^1 , Q^3 to Q^8 and Q^{10}) when it is

5 (3-7C)cycloalkenyl or for the (3-7C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for any one of the 'Q' groups (Q^1 , Q^3 to Q^{11}), G^2 or G^4 when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring

10 heteroatoms selected from oxygen, nitrogen and sulphur, which, unless specified otherwise, may be carbon or nitrogen linked. Examples of suitable values of "heteroaryl" include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, 1,3-benzodioxolyl, benzofuranyl, indolyl, benzothieryl, benzoxazolyl,

15 benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinoxalyl, cinnolyl or naphthyridinyl.

A suitable value for any one of the 'Q' groups (Q^1 , Q^3 to Q^{11}) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms

20 selected from oxygen, nitrogen and sulphur, which, unless specified otherwise, may be carbon or nitrogen linked. Examples of suitable values of "heterocyclyl" include oxiranyl, oxetanyl, azetidyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl,

25 dihydropyrimidinyl, tetrahydropyrimidinyl, tetrahydrothienyl, tetrahydrothiopyranyl, decahydroisoquinolyl or decahydroquinolyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,4-oxazepanyl, thiamorpholinyl 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl, more preferably tetrahydrofuran-3-yl, tetrahydropyran-4-yl, tetrahydrothien-3-yl, tetrahydrothiopyran-4-yl,

30 pyrrolidin-3-yl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-4-yl, piperidin-3-yl or piperazin-1-yl. A nitrogen or sulphur atom within a heterocyclyl group may be oxidized to give the corresponding N or S oxide, for example 1,1-dioxotetrahydrothienyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydrothiopyranyl or



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1-oxotetrahydrothiopyranyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidiny, 2-thioxopyrrolidiny, 2-oxoimidazolidiny, 2-thioxoimidazolidiny, 2-oxopiperidiny, 2,5-dioxopyrrolidiny, 2,5-dioxoimidazolidiny or 2,6-dioxopiperidiny.

5 A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

10 Suitable values for any of the 'R' groups (R^1 to R^{26}), or for various groups within an R^1 substituent, or for G^3 or for various groups within G^3 , or for any of the other 'G' groups (G^1 , G^2 or G^4) within Q^2 , or for various groups within Q^2 , or for Q^1 or for various groups within Q^1 , or for various groups within the Q^1 -Z- group include:-

- | | | |
|----|--|--|
| | for halogeno | fluoro, chloro, bromo and iodo; |
| 15 | for (1-6C)alkyl: | methyl, ethyl, propyl, isopropyl and ~~tert~~ -butyl; |
| | for (2-8C)alkenyl: | vinyl, isopropenyl, allyl and but-2-enyl; |
| | for (2-8C)alkynyl: | ethynyl, 2-propynyl and but-2-ynyl; |
| | for (1-6C)alkoxy: | methoxy, ethoxy, propoxy, isopropoxy and butoxy; |
| | for (2-6C)alkenyloxy: | vinylloxy and allyloxy; |
| 20 | for (2-6C)alkynyloxy: | ethynyloxy and 2-propynyloxy; |
| | for (1-6C)alkylthio: | methylthio, ethylthio and propylthio; |
| | for (1-6C)alkylsulphinyl: | methylsulphinyl and ethylsulphinyl; |
| | for (1-6C)alkylsulphonyl: | methylsulphonyl and ethylsulphonyl; |
| | for (1-6C)alkylamino: | methylamino, ethylamino, propylamino, |
| 25 | | isopropylamino and butylamino; |
| | for di-[(1-6C)alkyl]amino: | dimethylamino, diethylamino, <u>N</u> -ethyl-
<u>N</u> -methylamino and diisopropylamino; |
| | for (1-6C)alkoxycarbonyl: | methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl
and ~~tert~~ -butoxycarbonyl; |
| 30 | for <u>N</u> -(1-6C)alkylcarbamoyl: | <u>N</u> -methylcarbamoyl, <u>N</u> -ethylcarbamoyl and
<u>N</u> -propylcarbamoyl; |
| | for <u>N,N</u> -di-[(1-6C)alkyl]carbamoyl: | <u>N,N</u> -dimethylcarbamoyl, <u>N</u> -ethyl-
<u>N</u> -methylcarbamoyl and <u>N,N</u> -diethylcarbamoyl; |

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- for (2-6C)alkanoyl: acetyl and propionyl;
- for (2-6C)alkanoyloxy: acetoxy and propionyloxy;
- for (2-6C)alkanoylamino: acetamido and propionamido;
- for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;
- 5 for amino(2-6C)alkanoyl: aminoacetyl and 2-aminopropionyl;
- for N-(1-6C)alkylamino(2-6C)alkanoyl: N-methylaminoacetyl and 2-(N-methylaminopropionyl);
- for N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl: N,N-di-methylaminoacetyl;
- for N-(1-6C)alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl;
- 10 for N,N-di-[(1-6C)alkyl]sulphamoyl: N,N-dimethylsulphamoyl;
- for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;
- for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and N-methylethanesulphonylamino;
- for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;
- 15 for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;
- for (3-6C)alkynoylamino: propiolamido;
- for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;
- for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
- 20 for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;
- for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
- 25 for halogeno-(1-6C)alkyl: chloromethyl, 2-chloroethyl, 1-chloroethyl and 3-chloropropyl;
- for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
- 30 for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
- for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and

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- 3-cyanopropyl;
- for carboxy-(1-6C)alkyl: carboxymethyl, 2-carboxyethyl, 1-carboxyethyl and
3-carboxypropyl;
- for (1-6C)alkylthio-(1-6C)alkyl: methylthiomethyl, ethylthiomethyl,
5 2-methylthioethyl, 1-methylthioethyl and
3-methylthiopropyl;
- for (1-6C)alkylsulphinyl-(1-6C)alkyl: methylsulphinylmethyl, ethylsulphinylmethyl,
2-methylsulphinylethyl, 1-methylsulphinylethyl and
3-methylsulphinylpropyl;
- 10 for (1-6C)alkylsulphonyl-(1-6C)alkyl: methylsulphonylmethyl, ethylsulphonylmethyl,
2-methylsulphonylethyl, 1-methylsulphonylethyl and
3-methylsulphonylpropyl;
- for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and
2-acetamidoethyl;
- 15 for (1-6C)alkoxycarbonyl-(1-6C)alkyl: methoxycarbonylmethyl, 2-methoxycarbonylethyl
and 2-ethoxycarbonylethyl;
- for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl,
ethoxycarbonylaminomethyl,
20 tert-butoxycarbonylaminomethyl and
2-methoxycarbonylaminoethyl;
- for carbamoyl-(1-6C)alkyl: carbamoylmethyl, 1-carbamoylethyl,
2-carbamoylethyl and 3-carbamoylpropyl;
- for (2-6C)alkanoyl-(1-6C)alkyl: acetylmethyl and 2-acetylethyl;
- for N-(1-6C)alkylcarbamoyl-(1-6C)alkyl: N-methylcarbamoylmethyl,
25 N-ethylcarbamoylmethyl, N-propylcarbamoylmethyl,
1-(N-methylcarbamoyl)ethyl,
1-(N-ethylcarbamoyl)ethyl,
2-(N-methylcarbamoyl)ethyl,
2-(N-ethylcarbamoyl)ethyl and
30 3-(N-methylcarbamoyl)propyl; and
- for N,N-di[(1-6C)alkyl]carbamoyl-(1-6C)alkyl: N,N-dimethylcarbamoylmethyl,
N,N-diethylcarbamoylmethyl,

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2-(N,N-dimethylcarbamoyl)ethyl, and3-(N,N-dimethylcarbamoyl)propyl.

A suitable value for $(R^1)_m$ when it is a (1-3C)alkylenedioxy group is, for example, methylenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring
5 positions.

When in this specification reference is made to a (1-4C)alkyl group it is to be understood that such groups refer to alkyl groups containing up to 4 carbon atoms. A skilled person will realise that representative examples of such groups are those listed above under (1-6C)alkyl that contain up to 4 carbon atoms, such as methyl, ethyl, propyl and butyl.

10 Similarly, reference to a (1-3C)alkyl group refers to alkyl groups containing up to 3 carbon atoms such as methyl, ethyl and propyl. A similar convention is adopted for the other groups listed above such as (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl and (2-4C)alkanoyl.

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^3-X^1 - and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the
15 $OC(R^4)_2$ linking group which is attached to the quinazoline ring and the oxygen atom is attached to the Q^3 group. Similarly, when, for example a CH_3 group within a R^1 substituent bears a group of the formula $-X^3-Q^5$ and, for example, X^3 is a $C(R^7)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^7)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^5 group. A similar convention applies to the
20 attachment of the groups of the formulae Q^4-X^2 - and $-X^7-Q^7$.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, $CON(R^5)$, $N(R^5)$ or $C=C$. For example, insertion of a $C=C$ group into the ethylene chain within a 2-morpholinosthoxo group gives rise to a 4-morpholinobut-2-ynyloxy group and, for
25 example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group. It is to be understood that the term (2-6C)alkylene chain refers to any CH_2CH_2 group within R^1 and includes, for example alkylene chains within a (1-6C)alkyl, (1-6C)alkoxy, (2-8C)alkenyl, (2-8C)alkenyloxy, (2-8C)alkynyl and (2-8C)alkynyloxy group. For example the insertion of a
30 $N(CH_3)$ group between the third and fourth carbon atoms in a hex-5-enyloxy group in R^1 gives rise to a 3-(N-methyl-N-allylamino)propoxy group.



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When, as defined hereinbefore, any $\text{CH}_2=\text{CH}-$ or $\text{HC}\equiv\text{C}-$ group within a R^1 substituent optionally bears at the terminal $\text{CH}_2=$ or $\text{HC}\equiv$ position a substituent such as a group of the formula Q^4-X^2 wherein X^2 is, for example, NHCO and Q^4 is a heterocyclyl-(1-6C)alkyl group, suitable R^1 substituents so formed include, for example, N-[heterocyclyl-
 5 (1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl
 10 substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent as defined hereinbefore, suitable R^1 substituents so formed include, for example, hydroxy-substituted heterocyclyl-
 15 (1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocyclyl-
 20 (1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-
 25 2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocyclyl-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and
 30 3-morpholinopropylaminomethyl.

Similar considerations apply to the attachments and substitutions within the $-\text{Z}-\text{Q}^1$ group.

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It is to be understood that when, as defined hereinbefore, any CH₂ or CH₃ group within a R¹ substituent or a Q¹-Z- group optionally bears on each said CH₂ or CH₃ group a substituent as defined hereinbefore, the optional substituent may be present on any CH₂ or CH₃ group within a R¹ substituent or a Q¹-Z- group, including those on the hereinbefore defined substituents that may be present on an aryl, heteroaryl or heterocyclyl groups within R¹ or Q¹-Z-. For example, if Q¹ is a 1-(1-6C)alkyl-piperidin-4-yl group, the (1-6C)alkyl group may be optionally substituted by, for example a (2-6C)alkanoyl group to give a 1-((2-6C)alkanoyl-(1-6C)alkyl)-piperidin-4-yl group such as 1-(acetylmethyl)piperidin-4-yl or 1-(2-acetylethyl)piperidin-4-yl. Other suitable groups that may be so formed by Q¹ include,

10 (1-6C)alkoxycarbonyl-(1-6C)alkyl substituted heterocyclyl groups, such as 1-(methoxycarbonylmethyl)piperidin-4-yl or 1-(2-methoxycarbonylethyl)piperidin-4-yl, carbamoyl-(1-6C)alkyl substituted heterocyclyl groups such as 1-(carbamoylmethyl)piperidin-4-yl, or (1-6C)alkoxy-(1-6C)alkyl substituted heterocyclyl groups, such as 1-(2-methoxyethyl)piperidin-4-yl. Similarly when R¹ is a (1-6C)alkyl

15 substituted aryl, or heteroaryl group, the (1-6C)alkyl group may be optionally substituted by one of the hereinbefore defined substituents that may be present on a CH₂ or CH₃ group. For example if R¹ is a heteroaryl group substituted by (1-6C)alkylamino-(1-6C)alkyl, the terminal CH₃ group of the alkyl substituent may be further substituted by, for example, a(1-6C)alkylsulphonyl group. By way of example if R¹ is a 2-(ethylaminomethyl)-5-furyl

20 group, the ethyl group may be optionally substituted by a methylsulphonyl group to give a 2-(2-methylsulphonylethylaminomethyl)-5-furyl group.

Similar considerations apply to substituents that are optionally present on the terminal group of a CH₂=CH- or HC=C- group within a R¹ substituent or a Q¹-Z- group.

When, as defined hereinbefore, G³ and G⁴ together form, for example, a group of formula -O-CH=CH-, it is the oxygen atom, not the carbon atom, which is attached to the G³ para-position of the phenyl ring of formula Ia and the carbon atom is attached to the adjacent G⁴ meta-position of the phenyl ring of formula Ia.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition

30 salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a

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calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Particular novel compounds of the invention include, for example, quinazoline
 5 derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of m, R¹, R², R³, Z, L, Q¹ and Q² has any of the meanings defined hereinbefore or in paragraphs (a) to (www) hereinafter :-

- (a) each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl,
 10 (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino and N-(1-6C)alkyl-(3-6C)alkynoylamino, or from a group of the formula :

15 Q^3-X^1-

wherein X¹ is a direct bond or is selected from O, N(R⁴), CON(R⁴), N(R⁴)CO and OC(R⁴)₂ wherein R⁴ is hydrogen or (1-6C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent
 20 are optionally separated by the insertion into the chain of a group selected from O, N(R⁵), CON(R⁵), N(R⁵)CO, CH=CH and C≡C wherein R⁵ is hydrogen or (1-6C)alkyl,

and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl,
 25 (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :

Q^4-X^2-

wherein X² is a direct bond or is CO or N(R⁶)CO, wherein R⁶ is hydrogen or (1-6C)alkyl, and Q⁴ is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

30 and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, (1-6C)alkoxy,

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(1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :



wherein X^3 is a direct bond or is selected from O, $N(R^7)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$,

5 wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

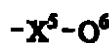
and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy,

10 (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :



wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or

15 (1-6C)alkyl, and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :



wherein X^5 is a direct bond or is selected from O and $N(R^{10})$, wherein R^{10} is hydrogen or

20 (1-6C)alkyl, and Q^6 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

25 (b) each R^1 group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :

30 Q^3-X^1-

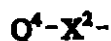
wherein X^1 is a direct bond or is selected from O, NH, CONH, NHCO and OCH_2 and Q^3 is phenyl, benzyl, cyclopropylmethyl, 2- or 3-thienyl, 2- or 3-thienylmethyl, 2-(2- or 3-thienyl)ethyl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-2-ylmethyl,

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2-(tetrahydrothien-2-yl)ethyl, tetrahydrothien-3-ylmethyl, 2-(tetrahydrothien-3-yl)ethyl, 2- or 3-furyl, furfuryl, 2-(2-furyl)ethyl, 3-furylmethyl, 2-(3-furyl)ethyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofurfuryl, 2-(tetrahydrofuran-2-yl)ethyl, tetrahydrofuran-3-ylmethyl, 2-(tetrahydrofuran-3-yl)ethyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperidin-3-ylethyl, 2-piperidin-4-ylethyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl, and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(CH₃), CONH, NHCO, CH=CH and C≡C,

and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of the formula :



wherein X² is a direct bond or is CO, NHCO or N(CH₃)CO and Q⁴ is 2-, 3- or 4-pyridyl, 2-, 3- or 4-pyridylmethyl, 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl,

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- 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl,
 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl,
 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl,
 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or
 5 4-piperazin-1-ylbutyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each
 said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy,
 methylsulphonyl, methylamino and dimethylamino, or from a group of the formula :



- 10 wherein X^3 is a direct bond or is selected from O, NH, $\text{N}(\text{CH}_3)$, CONH, NHCO and CH_2O and
 Q^5 is 2- or 3-furyl, furfuryl, 2-(2-furyl)ethyl, 3-furylmethyl, (3-furyl)ethyl,
 tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofurfuryl, 2-(tetrahydrofuran-2-yl)ethyl,
 tetrahydrofuran-3-ylmethyl, 2-(tetrahydrofuran-3-yl)ethyl 2-, 3- or 4-pyridyl, 2-, 3- or
 4-pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl,
 15 piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl,
 pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl,
 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl,
 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or
 3-piperazin-1-ylpropyl,

- 20 and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1
 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from
 fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methylamino,
 dimethylamino and methoxy,
 or optionally bears 1 substituent selected from a group of the formula :

- 25
$$-\text{X}^4-\text{R}^6$$

- wherein X^4 is a direct bond or is selected from O and NH, and R^6 is 2-hydroxyethyl,
 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, aminomethyl, 2-aminoethyl,
 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl,
 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl,
 30 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl,
 ethoxycarbonylaminomethyl or ~~tert~~-butoxycarbonylaminomethyl, and from a group of the
 formula :



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- wherein X^3 is a direct bond or is selected from O and NH, and Q^6 is pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofurfuryl, 2-(tetrahydrofuran-2-yl)ethyl,
- 5 tetrahydrofuran-3-ylmethyl, 2-(tetrahydrofuran-3-yl)ethyl, piperidin-4-yl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,
- and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2
- 10 oxo substituents;
- (c) m is 1 or 2 and the R^1 groups, which may be the same or different, are located at the 6- and/or 7-positions and are selected from hydroxy, amino, methyl, ethyl, propyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, benzyloxy, cyclopropylmethoxy, 2-cyclopropylethoxy,
- 15 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, tetrahydrofurfuryloxy, 2-(tetrahydrofuran-2-yl)ethoxy, 3-(tetrahydrofuran-2-yl)propoxy,
- 20 2-(tetrahydrofuran-3-yl)ethoxy, 3-(tetrahydrofuran-3-yl)propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
- 25 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, pyrrolidin-3-ylamino,
- 30 pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, piperidin-3-ylamino,

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piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino, 2-homopiperazin-1-ylethylamino, 3-homopiperazin-1-ylpropylamino, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-furyl, 3-furyl, tetrahydrofuran-2-yl and tetrahydrofuran-2-yl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(CH₃), CH=CH and C≡C,

and when R¹ is a vinyl or ethynyl group, the R¹ substituent optionally bears at the terminal CH₂= or HC≡ position a substituent selected from

N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and

4-dimethylaminobutyl, or from a group of the formula :



wherein X² is a direct bond or is NHCO or N(CH₃)CO and Q⁴ is imidazolylmethyl, 2-imidazolethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any phenyl, pyridyl, furyl or heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methylamino, ethylamino, dimethylamino, diethylamino, carbamoyl, methyl, ethyl, n-propyl, isopropyl and methoxy, and any piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-piperazin-1-ylethylamino,

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3-piperazin-1-ylpropylamino, or piperazin-1-yl group within a R^1 substituent is optionally N-substituted with 2-methoxyethyl, 3-methoxypropyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

- 10 (d) m is 1 and the R^1 group is located at the 7-position and is selected from methyl, ethyl, propyl, butyl, pentyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, amino, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, N-propyl-N-methylamino, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido, propiolamido, pyrrolidin-1-yl, piperidino, homopiperidin-1-yl, 15 morpholino, 1,4-oxazepan-4-yl, thiamorpholino, piperazin-1-yl and homopiperazin-1-yl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, $N(CH_3)$, CO, CONH and NHCO,

- and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each 20 said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, ethylsulphonyl, methylamino, ethylamino, dimethylamino and dimethylamino, or from a group of the formula:



- wherein X^3 is a direct bond or is selected from O, NH, $N(CH_3)$, CO, NHCO and CONH, and 25 Q^5 is phenyl, benzyl, 2-phenylethyl, 2-furyl, furfuryl, 2-(2-furyl)ethyl, 3-furyl, 2-(3-furyl)ethyl, 2-pyridyl, 2-pyridylmethyl, 2-(2-pyridyl)ethyl, 3-pyridyl, 3-pyridylmethyl, 2-(3-pyridyl)ethyl, 4-pyridyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl, 2-pyrimidinyl, 2-pyrimidinylmethyl, 2-(2-pyrimidinyl)ethyl, 4-pyrimidinyl, 4-pyrimidinylmethyl, 2-(4-pyrimidinyl)ethyl, 5-pyrimidinyl, 5-pyrimidinylmethyl, 2-(5-pyrimidinyl)ethyl, tetrahydrofuran-2-yl, 30 tetrahydrofurfuryl, 2-tetrahydrofuran-2-ylethyl, tetrahydrofuran-3-yl, tetrahydrofuran-3-ylmethyl, 2-tetrahydrofuran-3-ylethyl, pyrrolidin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, pyrrolidin-2-yl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, pyrrolidin-3-yl, pyrrolidin-3-ylmethyl, 2-pyrrolidin-3-ylethyl,

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morpholino, morpholinomethyl, 2-morpholinoethyl, piperidino, piperidinomethyl, 2-piperidinoethyl, piperidin-3-yl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-yl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, homopiperidin-1-yl, homopiperidin-1-ylmethyl, 2-homopiperidin-1-ylethyl, piperazin-1-yl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 5 homopiperazin-1-yl, homopiperazin-1-ylmethyl and 2-homopiperazin-1-ylethyl, and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methylamino, dimethylamino and methoxy,

10 or optionally bears 1 substituent selected from a group of the formula :



wherein X⁴ is a direct bond or is selected from O and NH and R⁸ is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 15 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

20 (e) m is 1 and the R¹ group is located at the 7-position and is selected from trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, pentyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, propylmethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido, propiolamido, pyrrolidin-1-yl, 25 piperidino, homopiperidin-1-yl, morpholino, thiamorpholino, piperazin-1-yl and homopiperazin-1-yl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(CH₃), CO, CONH and NHCO,

30 and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, and dimethylamino, or from a group of the formula:



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wherein X^3 is a direct bond or is selected from O, NH and N(CH₃) and Q^3 is selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, homopiperidin-1-yl, piperazin-1-yl homopiperazin-1-yl, phenyl, (2-, 3- or 4-)pyridyl and (2-, 4- or 5-)pyrimidinyl,

- 5 and wherein any phenyl, pyridyl, pyrimidinyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy, 2-methoxyethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 3-methoxypropoxy, aminomethoxy, 2-aminoethoxy, 3-aminopropoxy, methylaminomethoxy,
- 10 2-methylaminoethoxy, 2-ethylaminoethoxy, dimethylaminomethoxy, 2-dimethylaminoethoxy, amino, methylamino, dimethylamino, and wherein any pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl or homopiperazinyl moiety within R^1 is optionally further substituted on an available nitrogen atom with a substituent selected from tetrahydrofurfuryl, tetrahydrofuran-3-ylmethyl, 1-methylpiperidin-4-yl 1-ethylpiperidin-4-yl,
- 15 1-methylpiperidin-3-yl 1-ethylpiperidin-3-yl and 2-morpholinoethyl, and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;
- (f) m is 1 and the R^1 group is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, methylamino,
- 20 ethylamino, propylamino, dimethylamino, diethylamino, N-propyl-N-methylamino, acetamido, propionamido, benzyloxy, pyrrolidin-1-yl, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy,
- 25 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy,
- 30 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy or 3-homopiperazin-1-ylpropoxy,

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and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, $N(CH_3)$, $CH=CH$ and $C=C$,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each
5 said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino and dimethylamino,

and wherein any phenyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylamino and dimethylamino,

10 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

(g) m is 1 and the R^1 group is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, pyrrolidin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy,
15 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy, 3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy

and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R^1 substituent
20 are optionally separated by the insertion into the chain of a group selected from O, NH and $N(CH_3)$,

and wherein any terminal CH_3 group within a (1-6C)alkoxy chain in a R^1 substituent optionally bears on the terminal CH_3 group a substituent selected from hydroxy, amino and N-(1-methylpyrrolidin-3-yl)-N-methylamino,

25 and wherein any pyrrolidinyl or piperidinyl group within a R^1 substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,

and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl, 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl;

30 (h) m is 0;

(i) m is 1 and R^1 is located at the 7-position;

(j) R^3 is hydrogen;

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- (k) L is a direct bond or $\text{CH}(\text{R}^{22})$, wherein R^{22} is hydrogen, methyl or ethyl;
- (l) Z is a direct bond or is selected from O, S, SO, SO_2 , $\text{N}(\text{R}^{11})$ and CO;
- (m) Z is selected from $\text{CON}(\text{R}^{11})$, $\text{N}(\text{R}^{11})\text{CO}$, $\text{SO}_2\text{N}(\text{R}^{11})$, $\text{N}(\text{R}^{11})\text{SO}_2$, $\text{OC}(\text{R}^{11})_2$, $\text{SC}(\text{R}^{11})_2$ and $\text{N}(\text{R}^{11})\text{C}(\text{R}^{11})_2$, wherein R^{11} is hydrogen or (1-6C)alkyl;
- 5 (n) Z is O;
- (o) Z is a direct bond or is selected from O, S, SO, SO_2 , $\text{N}(\text{R}^{11})$ and CO wherein R^{11} is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q^1 -Z-
- 10 group are optionally separated by the insertion into the chain of a group selected from O, $\text{N}(\text{R}^{12})$, $\text{CON}(\text{R}^{12})$, $\text{N}(\text{R}^{12})\text{CO}$, $\text{CH}=\text{CH}$ and $\text{C}=\text{C}$ wherein R^{12} is hydrogen or (1-6C)alkyl, and wherein any CH_2 or CH_3 group within the Q^1 -Z- group optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the
- 15 formula :



wherein X^7 is a direct bond or is selected from O, $\text{N}(\text{R}^{14})$, $\text{CON}(\text{R}^{14})$, $\text{N}(\text{R}^{14})\text{CO}$ and $\text{C}(\text{R}^{14})_2\text{O}$, wherein R^{14} is hydrogen or (1-6C)alkyl, and Q^8 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- 20 and wherein any aryl, heteroaryl or heterocyclyl group within the Q^1 -Z- group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)alkyl, (1-6C)alkoxy, (1-4C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl and N,N-di-[(1-6C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :



wherein X^8 is a direct bond or is selected from O and $\text{N}(\text{R}^{16})$, wherein R^{16} is hydrogen or (1-6C)alkyl, and R^{15} is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl or a group of the formula :



wherein X^9 is a direct bond or is selected from O and $\text{N}(\text{R}^{17})$, wherein R^{17} is hydrogen or (1-6C)alkyl, and Q^9 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2

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substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

- 5 (p) the Q¹-Z- group is selected from cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy,
- or Z is a direct bond or is selected from O, S, SO, SO₂ and NH and Q¹ is phenyl, benzyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl,
- 10 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazol-1-yl)ethyl, 2-(1,2,4-triazol-1-yl)ethyl, 3-(1,2,3-triazol-1-yl)propyl, 3-(1,2,4-triazol-1-yl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, oxetan-3-yl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyranyl, 3- or 4-oxepanyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino,
- 15 piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, azetidin-3-yl, tetrahydrothien-3-yl, 1,1-dioxotetrahydrothien-3-yl, 1-oxotetrahydrothien-3-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, 1-oxotetrahydrothiopyran-3-yl, 1,1-dioxotetrahydrothiopyran-3-yl, 1-oxotetrahydrothiopyran-4-yl, 1,1-dioxotetrahydrothiopyran-4-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl,
- 20 piperidinomethyl, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperidin-3-ylethyl, 2-piperidin-4-ylethyl, 2-homopiperidin-1-ylethyl,
- 25 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q¹-Z- group are optionally separated by the insertion into the chain of a group selected from O, NH, CONH, NHCO, CH=CH and C≡C,

- 30 and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino and dimethylamino, or from a group of the formula :

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 $-X^7-Q^8$

wherein X^7 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^8 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl,
 5 pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any aryl, heteroaryl or heterocyclyl group within the Q^1-Z group
 10 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl and methoxy, or optionally bears 1 substituent selected from a group of the formula :

 $-X^8-R^{15}$

wherein X^8 is a direct bond or is selected from O and NH and R^{15} is 2-hydroxyethyl,
 15 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the
 20 formula :

 $-X^9-Q^9$

wherein X^9 is a direct bond or is selected from O and NH and Q^9 is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl,
 25 piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within the Q^1-Z group optionally bears 1 or 2 oxo substituents;

30 (q) the Q^1-Z group is selected from cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, phenoxy, phenylthio, anilino, benzyloxy, cyclopropylmethoxy, tetrahydrofuran-3-yloxy, tetrahydrofurfuryloxy, 3- or 4-tetrahydropyranyloxy, 2-tetrahydropyran-4-ylethoxy, 2-tetrahydropyran-3-ylethoxy, 3-tetrahydropyran-4-ylpropoxy,

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- 3-tetrahydropyran-3-ylpropoxy, tetrahydrothiopyran-3-yloxy,
2-tetrahydrothiopyran-3-ylethoxy, tetrahydrothiopyran-4-yloxy,
2-tetrahydrothiopyran-4-ylethoxy, 1-oxotetrahydrothiopyran-3-yloxy,
2-(1-oxotetrahydrothiopyran-3-yl)ethoxy, 1,1-dioxotetrahydrothiopyran-3-yloxy,
5 2-(1,1-dioxotetrahydrothiopyran-3-yl)ethoxy, 1-oxotetrahydrothiopyran-4-yloxy,
2-(1-oxotetrahydrothiopyran-4-yl)ethoxy, 1,1-dioxotetrahydrothiopyran-4-yloxy,
2-(1,1-dioxotetrahydrothiopyran-4-yl)ethoxy, 3-tetrahydrothiopyran-3-ylpropoxy,
3-(1,1-dioxotetrahydrothiopyran-3-yl)propoxy, 3-(1-oxotetrahydrothiopyran-3-yl)propoxy,
3-tetrahydrothiopyran-4-ylpropoxy, 3-(1-oxotetrahydrothiopyran-4-yl)propoxy,
10 3-(1,1-dioxotetrahydrothiopyran-4-yl)propoxy, tetrahydrothien-3-yloxy,
1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy,
2-tetrahydrothien-3-ylethoxy, 2-(1,1-dioxotetrahydrothien-3-yl)ethoxy,
2-(1-oxotetrahydrothien-3-yl)ethoxy, 3-tetrahydrothien-3-ylpropoxy,
3-(1,1-dioxotetrahydrothien-3-yl)propoxy, 3-(1-oxotetrahydrothien-3-yl)propoxy,
15 azetidin-3-yloxy, 2-azetidin-3-ylethoxy, 3-azetidin-3-ylpropoxy, 2-imidazol-1-ylethoxy,
3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 2-(1,2,4-triazol-1-yl)ethoxy,
3-(1,2,3-triazol-1-yl)propoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrrolidin-1-yl, morpholino,
piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,
pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,
20 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy,
2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy,
3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy,
2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy,
25 homopiperidin-3-yloxy, homopiperidin-4-yloxy, homopiperidin-3-ylmethoxy,
2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-piperazin-1-ylethoxy,
3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy,
2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, pyrrolidin-3-ylamino,
pyrrolidin-2-ylmethylanino, 2-pyrrolidin-2-ylethylanino, 3-pyrrolidin-2-ylpropylanino,
30 2-morpholinoethylamino, 3-morpholinopropylanino,
2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino,
3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylanino, 2-piperidinoethylamino,
3-piperidinopropylanino, piperidin-3-ylamino, piperidin-4-ylamino,

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piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino,
2-piperidin-4-ylethylamino, homopiperidin-3-ylamino, homopiperidin-4-ylamino,
homopiperidin-3-ylmethylamino, 2-homopiperidin-1-ylethylamino,
3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino,
5 2-homopiperazin-1-ylethylamino or 3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q¹-Z-
group are optionally separated by the insertion into the chain of a group selected from O, NH,
CH=CH and C=C,

and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each
10 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
methylsulphonyl, methylamino and dimethylamino,

and wherein any phenyl or heterocyclyl group within the Q¹-Z group optionally bears
1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,
trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl and methoxy, and a
15 piperidin-3-ylmethyl or piperidin-4-ylmethyl group within the Q¹-Z group is optionally
N-substituted with 2-methoxyethyl, 3-methoxypropyl, 2-aminoethyl, 3-aminopropyl,
2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl,
2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl,
2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last
20 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or
different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within the Q¹-Z group optionally bears 1 or 2 oxo
substituents;

(r) the Q¹-Z- group is selected from cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy,
25 tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy,
tetrahydropyran-4-yloxy, tetrahydrothiopyran-3-yloxy, 1-oxotetrahydrothiopyran-3-yloxy,
1,1-dioxotetrahydrothiopyran-3-yloxy, tetrahydrothiopyran-4-yloxy,
1-oxotetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy,
tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, .
30 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy,
3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy,
2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy,

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- 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy,
- 5 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy, homopiperidin-3-ylmethoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,
- and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
- 10 methylsulphonyl, methylamino and dimethylamino,
- and wherein any phenyl or heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,
- and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo
- 15 substituents;
- (a) the Q¹-Z- group is selected from cyclopentyloxy, cyclohexyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-3-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-3-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy,
- 20 1-oxotetrahydrothiopyran-3-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy and azetidin-3-yloxy,
- and wherein any azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within
- 25 the Q¹-Z- group is optionally N- substituted by a substituent selected from (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl and (1-4C)alkylsulphonyl,
- and wherein adjacent carbon atoms in any (2-4C)alkylene chain within the N- substituent are optionally separated by the insertion into the chain of a group selected from O,
- 30 NH and CO,
- and wherein any CH₂ or CH₃ group within the N- substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methylamino,

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di-methylamino, ethylamino, diethylamino, carbamoyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetyl, methoxycarbonyl and ethoxycarbonyl,

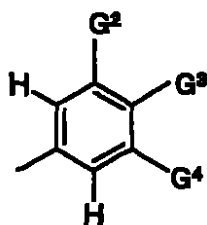
and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

- 5 (i) the Q¹-Z- group is selected from cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, 10 homopiperidin-4-yloxy and azetidin-3-yloxy,

and wherein the azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within the Q¹-Z- group is optionally N- substituted by a substituent selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, allyl, 2-propynyl, acetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, 15 N,N-di-methylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-di-methylcarbamoyl)ethyl, acetylmethyl, 2-acetylethyl, methoxycarbonylmethyl and 2-methoxycarbonylethyl,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

- (u) Q² is an aryl group of formula Ib



Ib

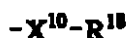
wherein G² and G⁴ each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and

- 25 di-[(1-6C)alkyl]amino,

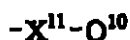
G³ is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl,

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(1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkenoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, 5 N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^{10} is a direct bond or is selected from O and N(R^{18}), wherein R^{18} is hydrogen or 10 (1-6C)alkyl, and R^{18} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X^{11} is a direct bond or is selected from O, S, SO, SO₂, N(R^{20}), CO, CH(OR^{20}), 15 CON(R^{20}), N(R^{20})CO, SO₂N(R^{20}), N(R^{20})SO₂, C(R^{20})₂O, C(R^{20})₂S and N(R^{20})C(R^{20})₂, wherein R^{20} is hydrogen or (1-6C)alkyl, and Q^{10} is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein Q^{10} optionally bears 1, 2 or 3 substituents, which may be the same or 20 different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenoyloxy, (2-6C)alkynoyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, 25 N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein any heterocyclyl group within Q^{10} optionally bears 1 or 2 oxo or thioxo substituents,

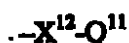
30 and provided that at least one of G^2 , G^3 and G^4 is other than hydrogen,

or G^3 and G^4 together form a group of formula :- CH=CH-CH=CH-,
-N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-,
-CH=N-CH=N-, -N=CH-CH=N-, -N=N-CH=CH-, -CH=CH-N=N-, -CH=CH-O-,

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-O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH₂-CH₂-O-, -O-CH₂-CH₂-, -CH₂-CH₂-S-,
 -S-CH₂-CH₂-, -O-CH₂-O-, -O-CH₂-CH₂-O-, -S-CH₂-S-, -S-CH₂-CH₂-S-, -CH=CH-NH-,
 -NH-CH=CH-, -CH₂-CH₂-NH-, -NH-CH₂-CH₂-, -N=CH-NH-, -NH-CH=N-, -NH-CH₂-NH-,
 -O-CH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH₂-NH-, -NH-CH₂-O-, -S-CH₂-NH-,
 5 -NH-CH₂-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -CH=N-S-, -O-NH-CH₂-, -CH₂-NH-O-,
 -S-NH-CH₂-, -CH₂-NH-S-, -NH-N=CH-, -CH=N-NH-, -NH-NH-CH₂-, -CH₂-NH-NH-,
 -N=N-NH- or -NH-N=N-,

and the 9- or 10-membered bicyclic heteroaryl or heterocyclic ring formed when G³
 and G⁴ together are linked optionally bears on the heteroaryl or heterocyclic portion of the
 10 bicyclic ring 1, 2 or 3 substituents, which may be the same or different, selected from
 halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl,
 (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of
 the formula:



15 wherein X¹² is a direct bond or is selected from O, SO, SO₂, N(R²¹) and CO, wherein R²¹ is
 hydrogen or (1-6C)alkyl and Q¹¹ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl,
 heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may
 be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy, and any
 bicyclic heterocyclic ring so formed optionally bears 1 or 2 oxo or thioxo groups;

20 (v) Q² is an aryl group of formula Ib wherein

G² is hydrogen,

G⁴ is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino,
 carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,
 (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

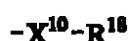
25 G³ is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino,
 carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,
 (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl,
 (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,
 N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl,

30 (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino,
 (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino,
 N-(1-6C)alkyl-(3-6C)alkynoylamino,

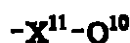
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N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^{10} is a direct bond or is selected from O and N(R^{19}), wherein R^{19} is hydrogen or
 5 (1-6C)alkyl, and R^{18} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X^{11} is a direct bond or is selected from O, S, SO, SO₂, N(R^{20}), CO, CH(OR²⁰),
 10 CON(R^{20}), N(R^{20})CO, SO₂N(R^{20}), N(R^{20})SO₂, C(R^{20})₂O, C(R^{20})₂S and N(R^{20})C(R^{20})₂, wherein R^{20} is hydrogen or (1-6C)alkyl, and Q^{10} is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein Q^{10} optionally bears 1, 2 or 3 substituents, which may be the same or
 15 different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
 20 N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein any heterocyclyl group within Q^{10} optionally bears 1 or 2 oxo or thioxo substituents,

25 and provided that at least one of G^3 and G^4 is other than hydrogen,

or G^3 and G^4 together form a group of formula :- -CH=CH-CH=CH-,

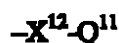
-N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-,
 -CH=N-CH=N-, -N=CH-CH=N-, -N=N-CH=CH-, -CH=CH-N=N-, -CH=CH-O-,
 -O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH₂-CH₂-O-, -O-CH₂-CH₂-, -CH₂-CH₂-S-,
 30 -S-CH₂-CH₂-, -O-CH₂-O-, -O-CH₂-CH₂-O-, -S-CH₂-S-, -S-CH₂-CH₂-S-, -CH=CH-NH-,
 -NH-CH=CH-, -CH₂-CH₂-NH-, -NH-CH₂-CH₂-, -N=CH-NH-, -NH-CH=N-, -NH-CH₂-NH-,
 -O-CH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH₂-NH-, -NH-CH₂-O-, -S-CH₂-NH-,
 -NH-CH₂-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -CH=N-S-, -O-NH-CH₂-, -CH₂-NH-O-,

NP
HSS

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-S-NH-CH₂-, -CH₂-NH-S-, -NH-N=CH-, -CH=N-NH-, -NH-NH-CH₂-, -CH₂-NH-NH-,
-N=N-NH- or -NH-N=N-,

and the 9- membered bicyclic heteroaryl or heterocyclic ring formed when G³ and G⁴ together are linked optionally bears on the heteroaryl or heterocyclic portion of the bicyclic
5 ring 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula:



wherein X¹² is a direct bond or is selected from O, SO, SO₂, N(R²¹) and CO, wherein R²¹ is
10 hydrogen or (1-6C)alkyl and Q¹¹ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy, and any bicyclic heterocyclic ring so formed optionally bears 1 or 2 oxo or thioxo groups;

(w) Q² is an aryl group of formula Ib wherein

15 G² is hydrogen,

G³ and G⁴ each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, , hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and provided that at least one of G³ and G⁴ is other than H;

20 (x) Q² is an aryl group of formula Ib wherein

G² is hydrogen,

G³ and G⁴ each independently is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

25 (y) Q² is an aryl group of formula Ib wherein G² is H and each of G³ and G⁴ independently is selected from hydrogen, halogeno, trifluoromethyl, (1-6C)alkyl, (2-8C)alkenyl and (2-8C)alkynyl,

and provided that at least one of G³ and G⁴ is other than H;

(z) Q² is an aryl group of formula Ib wherein G² is H and each of G³ and G⁴ independently

30 is selected from hydrogen, hydroxy, fluoro, chloro, bromo, trifluoromethyl, methyl, ethyl, vinyl, allyl, isopropenyl, ethynyl and 1-propynyl,

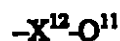
and provided that at least one of G³ and G⁴ is other than H;

NH
56

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(aa) Q^2 is an aryl group of formula Ib wherein G^3 and G^4 together form a group of formula:- $-\text{CH}=\text{CH}-\text{NH}-$, $-\text{NH}-\text{CH}=\text{CH}-$, $-\text{NH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-\text{NH}-$, $-\text{S}-\text{N}=\text{CH}-$ or $-\text{CH}=\text{N}-\text{S}-$,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 together are
5 linked optionally bears on the heteroaryl portion of the bicyclic ring 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula:



10 wherein X^{12} is a direct bond or is selected from O, SO, SO_2 , $\text{N}(\text{R}^{21})$ and CO, wherein R^{21} is hydrogen or (1-6C)alkyl and Q^{11} is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy, and any bicyclic heterocyclic ring so formed optionally bears 1 or 2 oxo or thioxo groups,

15 and G^2 is selected from hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(bb) Q^2 is an aryl group of formula Ib wherein G^3 and G^4 together form a group of formula:- $-\text{CH}=\text{CH}-\text{NH}-$, $-\text{NH}-\text{CH}=\text{CH}-$, $-\text{NH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-\text{NH}-$, $-\text{S}-\text{N}=\text{CH}-$ or $-\text{CH}=\text{N}-\text{S}-$

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 are linked
20 together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group selected from trifluoromethyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl and (1-4C)alkylsulphonyl, or from a group of the formula:



25 wherein X^{12} is a direct bond or is selected from SO_2 and CO, wherein R^{21} is hydrogen or (1-6C)alkyl and Q^{11} is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, which optionally bears 1 or 2 substituents, which may be the same or different, selected from cyano, halogeno, hydroxy, (1-6C)alkyl and (1-6C)alkoxy,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 together are
30 linked optionally bears on an available carbon atom in the heteroaryl portion of the bicyclic ring 1 substituent selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and

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di-[(1-6C)alkyl]amino, and any bicyclic heterocyclic ring so formed optionally bears 1 or 2 oxo or thioxo groups,

and G^2 is selected from hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

5 (cc) Q^2 is an aryl group of formula Ib wherein G^3 and G^4 together form a group of formula: -CH=CH-NH-, -NH-CH=CH-, -NH-N=CH- or -CH=N-NH-,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 are linked together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group of the formula:

10 $-X^{12}-Q^{11}$

wherein X^{12} is a direct bond or is selected from SO_2 and CO, wherein Q^{11} is phenyl, benzyl, 2-phenylethyl, 2-furyl, furfuryl, 3-furyl, 3-furylmethyl, 2-oxazolyl, 4-oxazolyl,

2-oxazolymethyl, 4-oxazolymethyl, 2-imidazolyl, 4-imidazolyl, 2-imidazolymethyl,

4-imidazolymethyl, 2-, 3- or 4-pyridyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl,

15 2-, 4- or 5- pyrimidinyl, 2-, 4- or 5- pyrimidinylmethyl, 2-(2-, 4- or 5- pyrimidinyl)ethyl,

1,2,4-triazol-3-yl, 1,2,4-triazol-5-ylmethyl, 1,2,4-triazol-3-ylmethyl, 1,2,4-triazol-5-yl

2-thienyl, 3-thienyl, 2-thienylmethyl, 3-thienylmethyl, 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl,

2-thiazolyl, 4-thiazolyl, 2-thiazolymethyl, 4-thiazolymethyl, 1,2,5-thiadiazol-3-yl,

1,2,5-thiadiazol-3-ylmethyl, 2-(1,2,5-thiadiazol-3-yl)ethyl which optionally bears 1 or 2

20 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, hydroxy, methyl and ethyl,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 together are linked optionally bears on an available carbon atom in the heteroaryl portion of the bicyclic ring 1 substituent selected from fluoro, chloro, bromo, cyano, hydroxy, amino, methyl, ethyl,

25 vinyl, ethynyl, methylamino and di-methylamino,

and G^2 is selected from hydrogen, fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl, vinyl, ethynyl, methylamino and di-methylamino;

(dd) Q^2 is an aryl group of formula Ib wherein G^3 and G^4 together form a group of formula: -NH-CH=CH- or -NH-N=CH-,

30 and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 are linked together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group of the formula:

$-X^{12}-Q^{11}$

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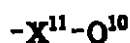
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wherein X^{12} is a direct bond or is SO_2 and Q^{11} is benzyl or 2-pyridylmethyl, which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, hydroxy and methyl,

and the 9- membered bicyclic heteroaryl ring formed when G^3 and G^4 together are
5 linked optionally bears at the 3-position in the heteroaryl portion of the bicyclic ring 1 substituent selected from fluoro, chloro, bromo, cyano, hydroxy, amino, methyl, ethyl and ethynyl,

and G^2 is selected from hydrogen, fluoro, chloro, bromo, cyano, hydroxy, amino, methyl, ethyl and ethynyl;

10 (ce) Q^2 is an aryl group of formula Ib wherein G^3 is selected from carbamoyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, or from a group of the formula :



wherein X^{11} is $CON(R^{20})$, wherein R^{20} is hydrogen or (1-6C)alkyl, and Q^{10} is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl,

15 (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein Q^{10} optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkynyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl,

20 (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N -(1-6C)alkyl-(2-6C)alkanoylamino, N -(1-6C)alkylsulphamoyl, N,N -di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N -(1-6C)alkyl-

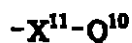
25 (1-6C)alkanesulphonylamino,

and wherein any heterocyclyl group within Q^{10} optionally bears 1 or 2 oxo or thioxo substituents,

and G^2 and G^4 each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl,

30 (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(ff) Q^2 is an aryl group of formula Ib wherein G^3 is selected from a group of the formula:





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wherein X^{11} is CO and Q^{10} is a 5 to 10 membered nitrogen containing heterocyclic group linked to X^{11} by a nitrogen atom,

and Q^{10} optionally bears 1 or 2 substituents selected from halogeno, cyano, hydroxy, amino, (1-6C)alkyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

5 and G^2 and G^4 each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(gg) Q^2 is an aryl group of formula Ib wherein G^3 is selected from a group of the formula:

$$-X^{11}-Q^{10}$$

10 wherein X^{11} is CO and Q^{10} is selected from, pyrrolidin-1-yl, piperidino, homopiperidino, morpholino, piperazin-1-yl, homopiperazin-1-yl, decahydroquinolin-1-yl, and decahydroisoquinolin-2-yl,

and wherein Q^{10} optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo, cyano, hydroxy, methyl and ethyl,

15 and G^2 and G^4 each independently is selected from hydrogen, fluoro, chloro, bromo, cyano, hydroxy, methyl, ethyl and ethynyl;

(hh) Q^2 is an aryl group of formula Ib wherein G^3 is selected from a group of the formula:

$$-X^{11}-Q^{10}$$

wherein X^{11} is a direct bond or is selected from O, S, SO, SO₂, N(R²⁰), CO, CH(OR²⁰),
 20 N(R²⁰)CO, SO₂N(R²⁰), N(R²⁰)SO₂, C(R²⁰)₂O, C(R²⁰)₂S and N(R²⁰)C(R²⁰)₂, wherein R²⁰ is hydrogen or (1-6C)alkyl, and Q^{10} is aryl, aryl-(1-6C)alkyl, heteroaryl and heteroaryl-(1-6C)alkyl,

and wherein Q^{10} optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, nitro, cyano, hydroxy, amino, (1-6C)alkyl,
 25 (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and G^2 and G^4 each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

(ii) Q^2 is an aryl group of formula Ib wherein G^3 is selected from a group of the formula:
 30
$$-X^{11}-Q^{10}$$

wherein X^{11} is a direct bond or is selected from O, S, SO₂, N(R²⁰), CO, CH(OR²⁰), C(R²⁰)₂O, C(R²⁰)₂NR²⁰, and C(R²⁰)₂S, wherein R²⁰ is hydrogen, methyl or ethyl, and Q^{10} is a phenyl, benzyl, 2-phenylethyl, naphthyl, naphthylmethyl or 2-naphthylethyl group which is optionally

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- substituted with 1 or 2 substituents selected from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl, isopropyl, vinyl, ethynyl and cyano,
- or Q^{10} is a heteroaryl moiety selected from furyl, furylmethyl, 2-(furyl)ethyl, thienyl, thienylmethyl, 2-(thienyl)ethyl, oxazolyl, oxazolymethyl, 2-(oxazolyl)ethyl, isoxazolyl, isoxazolymethyl, 2-(isoxazolyl)ethyl, imidazolyl, imidazolymethyl, 2-(imidazolyl)ethyl, thiazolyl, thiazolymethyl, 2-(thiazolyl)ethyl, 1,2,4-triazolyl, 1,2,4-triazolymethyl, 2-(1,2,4-triazolyl)ethyl, 1,2,5-thiadiazolyl, 1,2,5-thiadiazolymethyl, 2-(1,2,5-thiadiazolyl)ethyl, pyridyl, pyridylmethyl, 2-(pyridyl)ethyl, pyrimidinyl, pyrimidinylmethyl, 2-(pyrimidinyl)ethyl, 1,3-benzodioxolyl, 1,3-benzodioxolymethyl, 2-(1,3-benzodioxolyl)ethyl, quinolinyl, quinolinylmethyl, 2-(quinolinyl)ethyl, isoquinolinyl, isoquinolinylmethyl, 2-(isoquinolinyl)ethyl, quinazolinyl, quinazolinylmethyl and 2-(quinazolinyl)ethyl, which is optionally substituted with one or two substituents selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, ethyl, isopropyl, methoxy and ethoxy;
- and each of G^3 and G^4 independently is selected from hydrogen, fluoro, chloro, bromo, trifluoromethyl, methyl, ethyl, vinyl, allyl, ethynyl, methylamino and di-methylamino;
- (ii) Q^2 is an aryl group of formula Ib wherein G^3 is selected from a group of the formula:
- $$-X^{11}-Q^{10}$$
- wherein X^{11} is a direct bond or is selected from O, S, SO_2 , $N(R^{20})$, CO, $CH(OR^{20})$, $C(R^{20})_2O$, $C(R^{20})_2NR^{20}$, and $C(R^{20})_2S$, wherein R^{20} is hydrogen or methyl, and Q^{10} is a phenyl or benzyl group which is optionally substituted with 1 or 2 substituents selected from fluoro, chloro, bromo, nitro, trifluoromethyl, methyl, ethynyl and cyano,
- or Q^{10} is a heteroaryl moiety selected from 2-furyl, furfuryl, 3-furylmethyl, 2- or 3-thienyl, 2- or 3-thienylmethyl, 2-,4- or 5-oxazolyl, 2-,4- or 5-oxazolymethyl, 3-,4- or 5-isoxazolyl, 3-,4- or 5-isoxazolymethyl, 2-,4- or 5-1H-imidazolyl, 2-,4- or 5-1H-imidazolymethyl, 2-,4- or 5-thiazolyl, 2-,4- or 5-thiazolymethyl, 3- or 5-(1H-1,2,4-triazolyl), 3- or 5-(1H-1,2,4-triazolyl)methyl, 3- or 4-(1,2,5-thiadiazolyl), 3- or 4-(1,2,5-thiadiazolyl)methyl, 2- 3- or 4-pyridyl, 2-, 3- or 4-pyridylmethyl, 2-, 4- or 5-pyrimidinyl, 2-, 4- or 5-pyrimidinylmethyl, 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 1,3-benzodioxol-4-ylmethyl, 2-(1,3-benzodioxol-4-yl)ethyl, 2-(1,3-benzodioxol-5-yl)ethyl, 1,3-benzodioxolylmethyl 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinylmethyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinylmethyl, 2-, 3-, 4-, 5-, 6-, 7- or

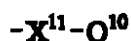


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8-quinazoliny and 2-, 3-, 4-, 5-, 6-, 7- or 8- quinazolinylmethyl, which is optionally substituted with one or two substituents selected from fluoro, chloro, bromo, methyl, ethyl, trifluoromethyl, ethynyl, and cyano;

and each of G^2 and G^4 independently is selected from hydrogen, fluoro, chloro, bromo, trifluoromethyl, methyl, ethyl, vinyl, allyl, ethynyl and cyano;

(kk) Q^2 is an aryl group of formula Ib wherein G^3 is selected from a group of the formula:



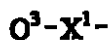
wherein X^{11} is a direct bond or is selected from O, S, $N(R^{20})$, CO, $CH(OR^{20})$ and $C(R^{20})_2NR^{20}$, wherein R^{20} is hydrogen or methyl, and Q^{10} is a phenyl or benzyl group which is

optionally substituted with 1 or 2 substituents selected from fluoro, chloro, bromo, nitro, methyl, ethyl, isopropyl, ethynyl and cyano,

or Q^{10} is a heteroaryl moiety selected from 2-1H-imidazolyl, 2-1H-imidazolylmethyl, 4-thiazolylmethyl, 2-thienylmethyl, 3-(1,2,5-thiadiazolyl), 3-(1,2,5-thiadiazolyl)methyl, 3-isoxazolylmethyl, 2- or 3-pyridyl, 2- or 3-pyridylmethyl, 8-quinoliny, and

8-quinolinylmethyl, which moiety is optionally substituted with one or two substituents selected from fluoro, chloro, bromo, trifluoromethyl, methyl, ethynyl and cyano; and each of G^2 and G^4 independently is selected from hydrogen, fluoro, chloro, bromo, methyl, and ethynyl;

(ll) m is 1 and the R^1 group is located at the 7-position and is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N -(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N -(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N -(1-6C)alkyl-(3-6C)alkynoylamino, N -(1-6C)alkylsulphamoyl, N,N -di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N -(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^1 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein each R^4 is, independently, hydrogen or (1-6C)alkyl, and Q^3 is (3-7C)cycloalkyl,

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(3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C=C wherein R⁵ is hydrogen or (1-6C)alkyl,

and wherein any CH₂=CH- or HC=C- group within a R^1 substituent optionally bears at the terminal CH₂= or HC= position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



wherein X² is a direct bond or is selected from CO and N(R⁶)CO, wherein R⁶ is hydrogen or (1-6C)alkyl, and Q⁴ is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH₂ or CH₃ group within a R^1 substituent optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X³ is a direct bond or is selected from O, S, SO, SO₂, N(R⁷), CO, CH(OR⁷), CON(R⁷), N(R⁷)CO, SO₂N(R⁷), N(R⁷)SO₂, C(R⁷)₂O, C(R⁷)₂S and N(R⁷)C(R⁷)₂, wherein R⁷ is hydrogen or (1-6C)alkyl, and Q⁵ (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl,

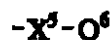
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- (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, 5 N-(1-6C)alkyl-(2-6C)alkanoylamino, amino(2-6C)alkanoyl, N-(1-6C)alkylamino(2-6C)alkanoyl, N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula:

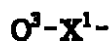


- 10 wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, 15 carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl, or from a group of the formula :



- 20 wherein X^5 is a direct bond or is selected from O, CO and $N(R^{10})$, wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^6 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and wherein any heterocyclyl group within R^1 optionally bears 1 or 2 oxo or thioxo 25 substituents;

(mm) m is 1 and the R^1 group is located at the 7-position and is selected from (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy, or from a group of the formula :



- 30 wherein X^1 is a direct bond or is O, and Q^3 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

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and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, $N(R^5)$, CO, $CH=CH$ and $C\equiv C$ wherein R^5 is hydrogen or (1-6C)alkyl,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each
 5 said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :

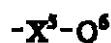


wherein X^3 is a direct bond or is selected from O and $N(R^7)$, wherein R^7 is hydrogen or
 10 (1-6C)alkyl, and Q^5 is heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, cyano, hydroxy, amino, carboxy, carbamoyl, formyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,
 15 N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, or from a group of the formula:



wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
 20 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N -(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N -di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X^5 is a direct bond and Q^6 is heterocyclyl or heterocyclyl-(1-6C)alkyl which
 25 optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group within R^1 optionally bears 1 or 2 oxo or thioxo substituents;

30 (nn) m is 1 and the R^1 group is located at the 7-position and is selected from (1-6C)alkoxy, (1-6C)alkenyloxy, (1-6C)alkynyloxy, or from a group of the formula :



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wherein X^1 is a direct bond or is O and Q^3 is tetrahydrofuran-3-yl, tetrahydrofurfuryl, 2-(tetrahydrofuran-2-yl)ethyl, tetrahydrofuran-3-ylmethyl, 2-(tetrahydrofuran-3-yl)ethyl, 1-, 2- or 3-pyrrolidinyl, morpholino, thiamorpholino, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, thiamorpholinomethyl, piperidinomethyl, 2-, 3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, piperazin-1-ylmethyl, homopiperazin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 2-pyrrolidin-2-ylethyl, 2-pyrrolidin-3-ylethyl, 3-pyrrolidin-1-ylpropyl, 3-pyrrolidin-2-ylpropyl, 3-pyrrolidin-3-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-thiamorpholinoethyl, 3-thiamorpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperidin-2-ylethyl, 2-piperidin-3-ylethyl, 2-piperidin-4-ylethyl, 3-piperidin-2-ylpropyl, 3-piperidin-3-ylpropyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl, and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, $N(CH_3)$, $CH=CH$ and $C\equiv C$, and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy, ethoxy, methylsulphonyl, methylamino and dimethylamino, or from a group of the formula :



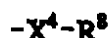
wherein X^5 is a direct bond or is selected from O, NH and $N(CH_3)$ and Q^5 is tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofurfuryl, 2-(tetrahydrofuran-2-yl)ethyl, tetrahydrofuran-3-ylmethyl, 2-(tetrahydrofuran-3-yl)ethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

and wherein any heterocyclyl group within R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, formyl, amino, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoyl, (1-4C)alkylsulphonyl,

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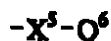
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(1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl and N,N-di-[(1-4C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :



wherein X^4 is a direct bond or is selected from O and NH, and R^8 is 2-hydroxyethyl,

- 5 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, fluoromethyl, 2-fluoroethyl, chloromethyl, 2-chloroethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetylmethyl, acetamidomethyl, carbamoylmethyl, 2-carbamoylethyl,
- 10 N-methylcarbamoylmethyl, N,N-di-methylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-di-methylcarbamoyl)ethyl, cyanomethyl, cyanoethyl, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, or from a group of the formula :



- 15 wherein X^5 is a direct bond or is selected from O and NH, and Q^6 is pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofurfuryl, 2-(tetrahydrofuran-2-yl)ethyl, tetrahydrofuran-3-ylmethyl, 2-(tetrahydrofuran-3-yl)ethyl, piperidin-4-yl, piperidinomethyl,
- 20 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, methyl, ethyl, methoxy, ethoxy, amino, methylamino and di-methylamino,

and wherein any heterocyclyl group within R^1 substituent optionally bears 1 oxo substituent;

- 25 (oo) m is 1 and the R^1 group is located at the 7-position and is a group of the formula :



wherein X^1 is a direct bond or is O and Q^3 is 1-, 2- or 3-pyrrolidinyl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, pyrrolidin-1-ylmethyl, pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl, 2-pyrrolidin-1-ylethyl,

- 30 2-pyrrolidin-2-ylethyl, 2-pyrrolidin-3-ylethyl, 3-pyrrolidin-1-ylpropyl, 3-pyrrolidin-2-ylpropyl, 3-pyrrolidin-3-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-2-ylmethyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-piperidin-2-ylethyl, 2-piperidin-3-ylethyl,

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2-piperidin-4-ylethyl, 3-piperidin-2-ylpropyl, 3-piperidin-3-ylpropyl, 3-piperidin-4-ylpropyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

- 5 and wherein any heterocyclyl group within R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, formyl, amino, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, (2-4C)alkanoyl, (1-4C)alkylsulphonyl, (1-4C)alkoxycarbonyl, N -(1-4C)alkylcarbamoyl and N,N -di-[(1-4C)alkyl]carbamoyl, or
- 10 optionally bears 1 substituent selected from a group of the formula :



wherein X^4 is a direct bond or is selected from O and NH, and R^8 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, fluoromethyl, 2-fluoroethyl, chloromethyl, 2-chloroethyl, aminomethyl, 2-aminoethyl,

- 15 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetylmethyl, acetamidomethyl, carbamoylmethyl, 2-carbamoylethyl, N,N -dimethylcarbamoylmethyl, 2-carbamoylethyl, 2-(N,N -dimethylcarbamoyl)ethyl, cyanomethyl, cyanoethyl, methoxycarbonylaminomethyl or ethoxycarbonylaminomethyl,
- 20 and wherein any heterocyclyl group within R^1 optionally bears 1 oxo substituent;
- (pp) m is 1 and the R^1 group is located at the 7-position and is a group of the formula :



wherein X^1 is O and Q^3 is selected from heterocyclyl-propyl or heterocyclyl-butyl, wherein said heterocyclyl group contains at least 1 nitrogen atom,

- 25 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, $N(R^5)$, CO, CH=CH and C=C wherein R^5 is hydrogen or (1-6C)alkyl,

- and wherein any heterocyclyl group within R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, carbamoyl, (1-4C)alkyl,
- 30 (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, (1-4C)alkylsulphonyl, (1-4C)alkoxycarbonyl, N -(1-4C)alkylcarbamoyl and N,N -di-[(1-4C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :

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 $-X^4-R^8$

- wherein X^4 is a direct bond or is selected from O and NH, and R^8 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, fluoromethyl, 2-fluoroethyl, chloromethyl, 2-chloroethyl, acetylmethyl, acetamidomethyl, carbamoylmethyl, 2-carbamoylethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-carbamoylethyl, 2-N-methylcarbamoylethyl, 2-(N,N-dimethylcarbamoyl)ethyl, cyanomethyl, cyanoethyl, methoxycarbonylaminomethyl or ethoxycarbonylaminomethyl, and wherein any heterocyclyl group within R^1 optionally bears 1 oxo substituent;
- (qq) m is 1 and the R^1 group is located at the 7-position and is selected from 3-pyrrolidin-1-ylpropoxy, 3-pyrrolidin-2-ylpropoxy, 3-pyrrolidin-3-ylpropoxy, 3-piperidinopropoxy, 3-piperidin-2-ylpropoxy, 3-piperidin-3-ylpropoxy, piperidin-4-ylpropoxy, 3-morpholinopropoxy, 3-morpholin-2-ylpropoxy, 3-morpholin-3-ylpropoxy, 3-piperazin-1-ylpropoxy and 3-piperazin-2-ylpropoxy, and wherein any heterocyclyl group within R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from hydroxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, (1-4C)alkylsulphonyl, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl and N,N-di-[(1-4C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :

 $-X^4-R^8$

20. wherein X^4 is a direct bond or is selected from O and NH, and R^8 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, fluoromethyl, 2-fluoroethyl, chloromethyl, 2-chloroethyl, acetylmethyl, acetamidomethyl, carbamoylmethyl, 2-carbamoylethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, cyanomethyl, cyanoethyl, methoxycarbonylaminomethyl or ethoxycarbonylaminomethyl, and wherein any heterocyclyl group within R^1 optionally bears 1 oxo substituent;
- (rr) m is 1 and the R^1 group is located at the 7-position and is selected from 3-pyrrolidin-1-ylpropoxy, 3-piperidinopropoxy, 3-morpholinopropoxy and 3-piperazin-1-ylpropoxy and wherein any heterocyclyl group within R^1 optionally bears a hydroxy substituent and
- 30 wherein any piperazinyl group in R^1 optionally bears a substituent selected from hydroxy, methyl, ethyl, isopropyl, acetyl, allyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-di-methylcarbamoylmethyl, acetylmethyl and cyanomethyl, and wherein any heterocyclyl group within R^1 optionally bears an oxo substituent;

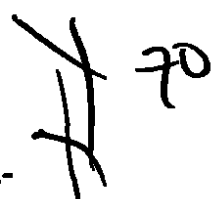
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- (ss) m is 1 and the R¹ group is located at the 7-position and is selected from 4-pyrrolidin-1-ylbutoxy, 4-pyrrolidin-2-ylbutoxy, 4-pyrrolidin-3-ylbutoxy, 4-piperidinobutoxy, 4-piperidin-2-ylbutoxy, 4-piperidin-3-ylbutoxy, 4-piperidin-4-ylbutoxy, 4-morpholinobutoxy, 4-morpholin-2-ylbutoxy, 4-morpholin-3-ylbutoxy, 4-piperazin-1-ylbutoxy and 4-piperazin-2-ylbutoxy, .
 5 and wherein any heterocyclyl group within R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from hydroxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, (1-4C)alkylsulphonyl, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl and N,N-di-[(1-4C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :



- wherein X⁴ is a direct bond or is selected from O and NH, and R⁸ is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, fluoromethyl, 2-fluoroethyl, chloromethyl, 2-chloroethyl, acetylmethyl, acetamidomethyl, carbamoylmethyl, 2-carbamoylethyl, N,N-dimethylcarbamoylmethyl, 2-carbamoylethyl,
 15 2-(N,N-dimethylcarbamoyl)ethyl, cyanomethyl, cyanoethyl, methoxycarbonylaminomethyl or ethoxycarbonylaminomethyl,
 and wherein any heterocyclyl group within R¹ optionally bears 1 oxo substituent;
 (tt) m is 1 and the R¹ group is located at the 7-position and is selected from 4-pyrrolidin-1-ylbutoxy, 4-piperidinobutoxy, 4-morpholinobutoxy and 4-piperazin-1-ylbutoxy,
 20 and wherein any heterocyclyl group within R¹ optionally bears a hydroxy substituent and wherein any piperazinyl group in R¹ optionally bears a substituent selected from hydroxy, methyl, ethyl, isopropyl, acetyl, allyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl and cyanomethyl,
 and wherein any heterocyclyl group within R¹ optionally bears an oxo substituent;
 25 (uu) m is 1 and the R¹ group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy and 3-piperazin-1-ylpropoxy,
 and wherein any piperazinyl group within R¹ optionally bears a substituent selected
 30 from hydroxy, methyl, ethyl, isopropyl, acetyl, allyl, 2-propynyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl and cyanomethyl,
 and wherein any heterocyclyl group within R¹ optionally bears an oxo substituent;



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(vv) m is 1 and the R¹ group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperazin-1-ylethoxy and 3-piperazin-1-ylpropoxy,

and wherein any piperazinyl group within R¹ optionally bears a substituent selected
5 from hydroxy, methyl, acetyl, allyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl and N,N-dimethylcarbamoylmethyl,

and wherein any heterocyclyl group within R¹ optionally bears an oxo substituent;

(ww) m is 1 and the R¹ group is located at the 7-position and is selected from 3-pyrrolidin-1-ylpropoxy and 3-morpholinopropoxy,

10 and wherein any heterocyclyl group within R¹ optionally bears an oxo substituent;

(xx) m is 1 and the R¹ group is located at the 7-position and is selected from methoxy, 2-methoxyethoxy, 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy and 3-piperazin-1-ylpropoxy,

and wherein any piperazinyl group within R¹ optionally bears a substituent selected from
15 carbamoylmethyl, N-methylcarbamoylmethyl and N,N-dimethylcarbamoylmethyl,

(yy) m is 1 and the R¹ group is located at the 7-position and is selected from (1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH and

20 N(CH₃),

and wherein any CH₃ group within a R¹ substituent optionally bears on each said CH₃ group a substituent selected from hydroxy, amino, methoxy, ethoxy, methylsulphonyl, methylamino and dimethylamino;

(zz) m is 1 and the R¹ group is located at the 7-position and is (1-3C)alkoxy or (1-3C)alkoxy(1-3C)alkoxy, for example methoxy, ethoxy and 2-methoxy;

(aaa) m is 1 and the R¹ group is located at the 7-position and is methoxy;

(bbb) Q¹ is (3-7C)cycloalkyl, (3-7C)cycloalkenyl or heterocyclyl,

and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent
30 selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-

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(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

- and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkythio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
- 10 N-(1-6C)alkyl-(2-6C)alkanoylamino, amino(2-6C)alkanoyl, N-(1-6C)alkylamino(2-6C)alkanoyl, N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- 15 wherein X⁸ is a direct bond or is selected from O and N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and R¹⁵ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl,
- 20 (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo or thioxo substituents;

(ccc) Q¹ is selected from (3-7C)cycloalkyl and a 4, 5, 6 or 7 membered heterocyclyl ring linked to Z by a carbon atom,

- 25 and wherein any NH group within a heterocyclyl group in Q¹ optionally bears a substituent selected from formyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, aminoalkanoyl, (1-4C)alkoxycarbonyl, carbamoyl, sulphamoyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-(1-4C)alkylsulphamoyl and (1-4C)alkylsulphonyl, or from a group of the formula :



wherein X⁸ is a direct bond, and R¹⁵ is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, carboxy-(1-6C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, carbamoyl-(1-4C)alkyl,

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N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]carbamoyl-(1-4C)alkyl, (2-4C)alkanoyl-(1-4C)alkyl or (1-4C)alkoxycarbonyl-(1-4C)alkyl,

- and wherein any CH or CH₂ group within a (3-7C)cycloalkyl or heterocyclyl group within Q¹ group optionally bears 1 substituent on each said CH group or 1 or 2 substituents on each said CH₂ group, which may be the same or different, selected from halogeno and (1-6C)alkyl, or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents,

- (ddd) Z is O and Q¹ is selected from a 4, 5 or 6 membered heterocyclyl ring containing at least 1 nitrogen, atom, said ring being linked to Z by a carbon atom, and wherein any NH group within a heterocyclyl group optionally bears a substituent selected from formyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, (1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-(1-4C)alkylsulphamoyl and (1-4C)alkylsulphonyl, or from a group of the formula :



- wherein X⁸ is a direct bond, and R¹⁵ is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, carboxy-(1-6C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]carbamoyl-(1-4C)alkyl, (2-4C)alkanoyl-(1-4C)alkyl or (1-4C)alkoxycarbonyl-(1-4C)alkyl,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

- (eee) Z is O and Q¹ is selected from azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl, (conveniently pyrrolidin-3-yl, piperidin-3-yl or piperidin-4-yl), and wherein any NH group within a heterocyclyl group in Q¹ optionally bears a substituent selected from formyl, cyano, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl,

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(1-4C)alkoxycarbonyl, carbamoyl, sulphamoyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl, N-(1-4C)alkylsulphamoyl, N,N-di-(1-4C)alkylsulphamoyl and (1-4C)alkylsulphonyl, or from a group of the formula :



5 wherein X^8 is a direct bond, and R^{15} is halogeno-(1-4C)alkyl, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, cyano-(1-4C)alkyl, carboxy-(1-4C)alkyl, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl, di-[(1-4C)alkyl]amino-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-[(1-4C)alkyl]carbamoyl-(1-4C)alkyl, (2-4C)alkanoyl-(1-4C)alkyl or (1-4C)alkoxycarbonyl-(1-4C)alkyl,

10 and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1 or 2 oxo substituents;

(fff) Z is O and Q^1 is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl, and wherein any NH group within a pyrrolidinyl or piperidinyl group in Q^1 optionally bears a substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl,

15 ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl and from a group of the formula:



wherein X^8 is a direct bond, and R^{15} is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methylcarbamoyl-(1-3C)alkyl,

20 N,N-di-methylcarbamoyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or methoxycarbonyl-(1-3C)alkyl, and wherein any pyrrolidinyl or piperidinyl group within the Q^1 -Z- group optionally bears 1 oxo substituent;

(ggg) Z is O and Q^1 is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl, and wherein any NH group within a pyrrolidinyl or piperidinyl group in Q^1 optionally bears a

25 substituent selected from methyl, ethyl, allyl, acetyl, carbamoyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, 2-fluoroethyl, methoxyethyl carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, acetylmethyl and methoxycarbonylmethyl,

and wherein any pyrrolidinyl or piperidinyl group within the Q^1 -Z- group optionally bears 1

30 oxo substituent;

(hhh) Z is O and Q^1 is selected from a 5 or 6 membered heterocyclyl ring containing at least 1 hetero atom selected from O and S and no nitrogen hetero atoms, and wherein said heterocyclyl ring is linked to Z by a carbon atom,

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and wherein said 5 or 6 membered heterocyclyl ring optionally bears 1, 2 or 3 substituents selected from halogeno, (1-6C)alkyl, hydroxy, amino, carboxy, (1-6C)alkoxy and (1-6C)alkylthio

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

(iii) Z is O and Q¹ is selected from tetrahydrofuran-3-yl, tetrahydropyran-3-yl and tetrahydropyran-4-yl,

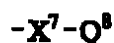
and wherein any tetrahydrofuranyl or tetrahydropyranyl group within Q¹ optionally bears 1 or 2 substituents selected from fluoro, chloro, hydroxy, methyl, ethyl and amino, and wherein any tetrahydrofuranyl or tetrahydropyranyl group within the Q¹-Z- group optionally bears 1 oxo substituent;

(iii) Z is O and Q¹ is selected from tetrahydrofuran-3-yl, tetrahydropyran-3-yl and tetrahydropyran-4-yl,

and wherein Q¹ optionally bears an oxo substituent;

(kkk) Z is O and Q¹ is selected from tetrahydrofuran-3-yl and piperidin-4-yl, and wherein any piperidin-4-yl group optionally bears a substituent at the 1-position selected from methyl, carbamoylmethyl, and N,N-dimethylcarbamoylmethyl;

(iii) Q¹ is (3-7C)cycloalkyl, which optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, and from a group of the formula:



wherein X⁵ is a direct bond or is selected from O, CO and N(R¹⁴), wherein R¹⁴ is hydrogen or (1-6C)alkyl, and Q⁸ is a nitrogen containing heterocyclyl or nitrogen containing heterocyclyl-(1-6C)alkyl, and wherein any heterocyclyl group in Q⁸ optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, amino, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

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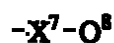
and wherein any heterocyclyl group in Q^1 optionally bears 1 or 2 oxo substituents;
 (mmm) Q^1 is selected (3-7C)cycloalkyl, which is substituted by 1 substituent selected from, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,

5 and from a group of the formula:



wherein X^5 is a direct bond or is selected from O and N(R^{10}), wherein R^{10} is hydrogen or (1-6C)alkyl, and Q^8 is nitrogen containing heterocyclyl or nitrogen containing heterocyclyl-(1-6C)alkyl, and wherein any heterocyclyl group in Q^8 optionally bears 1 or 2
 10 substituents, which may be the same or different, selected from hydroxy, (1-4C)alkyl, amino, (1-4C)alkylamino and di-[(1-4C)alkyl]amino,

and wherein any heterocyclyl group in Q^1 optionally bears 1 or 2 oxo substituents;
 (nnn) Z is O and Q^1 is (3-7C)cycloalkyl substituted by 1 substituent selected from, amino, (1-4C)alkylamino, di-[(1-4C)alkyl]amino, amino-(1-4C)alkyl, (1-4C)alkylamino-(1-4C)alkyl,
 15 di-[(1-4C)alkyl]amino-(1-4C)alkyl, and from a group of the formula:



wherein X^5 is a direct bond, and Q^6 is a 5 or 6 membered nitrogen containing heterocyclyl, and wherein Q^8 optionally bears 1 or 2 substituents, which may be the same or different, selected from methyl, ethyl, amino, methylamino, ethyl or dimethylamino,

20 and wherein any heterocyclyl group in Q^1 optionally bears 1 oxo substituent;
 (ooo) Z is O and Q^1 is selected from cyclopentyl and cyclohexyl, which is substituted by a substituent selected from pyrrolidin-1-yl, morpholino, piperidino and piperazin-1-yl, and wherein any pyrrolidinyl, morpholino, piperidino or piperazinyl group in Q^1 optionally bears 1 or 2 substituents selected from methyl, amino, methylamino, ethylamino and dimethylamino,

25 and wherein any heterocyclyl group in Q^1 optionally bears an oxo substituent;

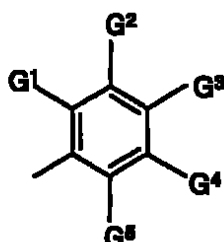
(ppp) Z is O and Q^1 is 4-(piperazin-1-yl)cyclohexyl, wherein the piperazin-1-yl group is optionally substituted at the 4-position by (1-3C)alkyl, for example methyl;

(qqq) Z is O and Q^1 is selected from piperidin-4-yl optionally substituted at the 1 position by a substituent selected from methyl, ethyl, allyl, acetyl, methoxycarbonylmethyl, methoxymethyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl,
 30 N,N-dimethylcarbamoylmethyl and acetylmethyl,

and wherein the piperidin-4-yl group optionally bears an oxo substituent;

(rrr) Q^1Z is 1-methylpiperidin-4-yloxy;

- (ss) Q^1Z is tetrahydrofuran-3-yloxy;
 (tt) Q^1Z is tetrahydropyran-4-yloxy;
 (uu) L is a direct bond;
 (vv) Q^2 is an aryl group of formula Ia



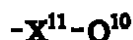
Ia

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wherein G^1 and G^5 are hydrogen,

G^2 and G^4 each independently is selected from hydrogen, halogeno, (1-6C)alkyl, (2-8C)alkenyl and (2-8C)alkynyl,

G^3 is selected from hydrogen, halogeno, hydroxy, (1-6C)alkyl, (2-8C)alkenyl and
 10 (2-8C)alkynyl, or from a group of the formula :



wherein X^{11} is a direct bond or is selected from O, S, SO_2 , $N(R^{20})$, CO, $C(R^{20})_2N(R^{20})$ and $N(R^{20})C(R^{20})_2$, wherein R^{20} is hydrogen or (1-6C)alkyl, and Q^{10} is aryl, aryl-(1-6C)alkyl, heteroaryl or heteroaryl-(1-6C)alkyl,

15 and wherein Q^{10} optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, formyl, carbamoyl, sulphonamoyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, (1-6C)alkylsulphonamoyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,
 20 N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N -(1-6C)alkyl-(2-6C)alkanoylamino, N -(1-6C)alkylsulphonamoyl, N,N -di-[(1-6C)alkyl]sulphonamoyl, (1-6C)alkanesulphonylamino and N -(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



25 wherein X^{13} is a direct bond or is selected from O and $N(R^{24})$, wherein R^{24} is hydrogen or (1-6C)alkyl, and R^{23} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,

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N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

and wherein any heterocyclyl group within Q^{10} optionally bears 1 or 2 oxo or thioxo substituents,

5 or G^3 and G^4 together form a group of formula :- $-NH-CH=CH-$ or $-NH-N=CH-$

and the 9- membered bicyclic heteroaryl ring formed when G^3 and G^4 together are linked optionally bears on the heteroaryl portion of the bicyclic ring 1 or 2 substituents, which may be the same or different, selected from halogeno, cyano, (1-6C)alkyl and a group of the formula:

10 $-X^{12}-Q^{11}$

wherein X^{12} is a direct bond or is selected from SO_2 , $N(R^{21})$, $SO_2N(R^{21})$ and CO, wherein R^{21} is hydrogen or (1-6C)alkyl and Q^{11} is aryl, aryl-(1-6C)alkyl, heteroaryl,

heteroaryl-(1-6C)alkyl, which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy,

15 formyl, carbamoyl, sulphonamoyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino,

20 N-(1-6C)alkylsulphonamoyl, N,N-di-[(1-6C)alkyl]sulphonamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$-X^{14}-R^{25}$

wherein X^{14} is a direct bond or is selected from O and $N(R^{26})$, wherein R^{26} is hydrogen or (1-6C)alkyl, and R^{25} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,

25 cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,

N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl,

with the proviso that G^2 , G^3 and G^4 are not all hydrogen;

30 (www) Q^2 is an aryl group of formula Ia as hereinbefore defined,

wherein G^1 , G^2 and G^5 are hydrogen,

G^3 and G^4 each independently is selected from hydrogen, halogeno, hydroxy, (1-6C)alkyl, (2-8C)alkenyl and (2-8C)alkynyl,

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with the proviso that both G^3 and G^4 are not hydrogen;

(xxx) Q^2 is an aryl group of formula Ia as hereinbefore defined,
wherein G^1 , G^2 , G^3 and G^5 are hydrogen, and

G^4 is selected from chloro, bromo, methyl and ethynyl

5 (yyy) Q^2 is an aryl group of formula Ia as hereinbefore defined,
wherein G^1 , G^2 and G^5 are hydrogen,

G^3 is selected from halogeno and hydroxy, and

G^4 is halogeno;

(zzz) Q^2 is an aryl group of formula Ia as hereinbefore defined,

10 wherein G^1 , G^2 and G^5 are hydrogen,

G^3 is selected from fluoro and hydroxy, and

G^4 is chloro;

(aaaa) the group $Q^2LN(R^3)$ is selected from 3-chloro-4-fluoroanilino, 3-chloro-4-hydroxyanilino, 3-fluoroanilino, 3-bromoanilino, 3-chloroanilino, 3-methylanilino and 3-

15 ethynylanilino;

(bbbb) the group $Q^2LN(R^3)$ is 3-chloro-4-fluoroanilino;

(cccc) the group $Q^2LN(R^3)$ is 3-bromoanilino;

(dddd) the group $Q^2LN(R^3)$ is 3-chloroanilino;

(eeee) the group $Q^2LN(R^3)$ is 3-methylanilino;

20 (ffff) the group $Q^2LN(R^3)$ is 3-ethynylanilino;

(gggg) Q^2 is an aryl group of formula Ia wherein:

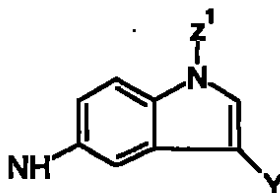
G^1 , G^2 and G^5 are hydrogen, and

G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$ or $-NH-N=CH-$,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 together are

25 linked optionally bears on the heteroaryl portion of the bicyclic ring 1 or 2 substituents, which may be the same or different, selected from halogeno, cyano and (1-6C)alkyl;

(hhhh) $Q^2LN(R^3)$ is a group of the formula Ic:



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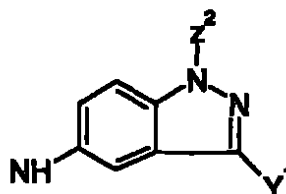
Ic

wherein Z^1 is hydrogen or (1-4C)alkyl, and

Y is selected from hydrogen, halogeno, (1-4C)alkyl and cyano;

(iii) $Q^2LN(R^3)$ is a group of the formula Id:

5



Id

wherein Z^2 is hydrogen or (1-4C)alkyl, and

Y^1 is selected from hydrogen and halogeno;

10 (iiii) $Q^2LN(R^3)$ is a group of the formula Ic as hereinbefore defined wherein Z^1 is hydrogen and Y^1 is selected from chloro and bromo;

(kkkk) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^3 are hydrogen, and

G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$, and the indolyl ring so

15 formed by G^3 and G^4 together with the carbon atoms to which they are attached is substituted at the 1-position by a group of the formula:



wherein X^{12} is a direct bond and Q^{11} is phenyl-(1-6C)alkyl or heteroaryl-(1-6C)alkyl, and

wherein any phenyl or heteroaryl group in Q^{11} optionally bears 1 or 2 substituents, which may

20 be the same or different, selected from selected from halogeno, cyano, hydroxy, amino,

carbamoyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,

(1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,

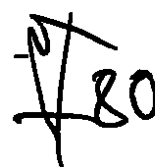
di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,

halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

25 amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl,

di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,

N-(1-6C)alkylcarbamoyl-(1-6C)alkyl and N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl.



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and wherein the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is optionally substituted at the 3-position by a substituent selected from halogeno, cyano and (1-6C)alkyl;

(III) Q^2 is a group of formula Ia wherein:

5 G^1 , G^2 and G^5 are hydrogen, and

G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$, and the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is substituted at the 1-position by a group of the formula:

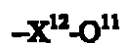


10 wherein X^{12} is a direct bond and Q^{11} is benzyl or heteroaryl-methyl, and wherein any phenyl or heteroaryl group in Q^{11} optionally bears 1 or 2 substituents, which may be the same or different, selected from selected from halogeno, cyano, hydroxy, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and
 15 and wherein the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is optionally substituted at the 3-position by halogeno;
 and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;

(mmmm) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen, and

20 G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$, and the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is substituted at the 1-position by a group of the formula:



wherein X^{12} is a direct bond and Q^{11} is benzyl which is optionally substituted by 1 or 2
 25 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, methyl and ethyl, (for example Q^{11} is 2-fluorobenzyl or 3-fluorobenzyl), and
 and wherein the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is optionally substituted at the 3-position by a substituent selected from chloro and bromo;

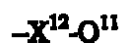
30 and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;

(nmn) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen, and

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G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$, and the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is substituted at the 1-position by a group of the formula:

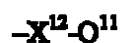


- 5 wherein X^{12} is a direct bond and Q^{11} furfuryl, 3-furylmethyl, 2-oxazolymethyl, 4-oxazolymethyl, 3-isoxazolymethyl, 5-isoxazolymethyl, 2-imidazolymethyl, 4-imidazolymethyl, 2-, 3- or 4-pyridylmethyl, 2-, 4- or 5-pyrimidinylmethyl, 1,2,4-triazol-5-ylmethyl, 1,2,4-triazol-3-ylmethyl, 1,2,4-triazol-5-ylmethyl, 2-thienylmethyl, 3-thienylmethyl, 2-thiazolymethyl, 4-thiazolymethyl, 1,2,5-thiadiazol-3-ylmethyl, and wherein any heteroaryl
- 10 group within Q^{11} optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and
- wherein the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is optionally substituted at the 3-position by halogeno;
- 15 and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;

(oooo) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen, and

- G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$, and the indolyl ring so
- 20 formed by G^3 and G^4 together with the carbon atoms to which they are attached is substituted at the 1-position by a group of the formula:



- wherein X^{12} is a direct bond and Q^{11} is 2-oxazolymethyl, 4-oxazolymethyl, 3-isoxazolymethyl, 5-isoxazolymethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl,
- 25 2-thiazolymethyl or 4-thiazolymethyl and wherein any heteroaryl group within Q^{11} optionally bears 1 or 2 substituents, which may be the same or different, selected from amino, methyl, ethyl, methylamino and dimethylamino;
- and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;

- 30 (pppp) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen, and

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G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$, and the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is substituted at the 1-position by a group of the formula:



- 5 wherein X^{12} is a direct bond and Q^{11} is 3-isoxazolylmethyl, 4-thiazolylmethyl or 2-pyridylmethyl, and wherein any heteroaryl group within Q^{11} optionally bears 1 or 2 substituents, which may be the same or different, selected from methyl and ethyl; and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;
- 10 (qqqq) Q^2 is a group of formula Ia wherein:
 G^1 , G^2 and G^3 are hydrogen,
 G^4 is selected from hydrogen, halogeno, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl and (2-6C)alkynyl, and
 G^5 is a group of the formula:

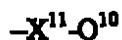


- 15 wherein X^{11} is O and Q^{10} is selected from phenyl-(1-6C)alkyl and heteroaryl-(1-6C)alkyl, and wherein any phenyl or heteroaryl group within Q^{10} optionally bears 1 or 2 substituents, which may be the same or different, selected from selected from halogeno, cyano, hydroxy, amino, carbamoyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl and
- 20 N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl;
 and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;

(mmr) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen,

- 30 G^4 is selected from hydrogen, halogeno, (1-6C)alkyl and (2-6C)alkynyl, and
 G^3 is a group of the formula:



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wherein X^{11} is O and Q^{10} is selected from benzyl and heteroaryl-methyl, and wherein any phenyl or heteroaryl group within Q^{10} optionally bears 1 or 2 substituents, which may be the same or different, selected from selected from halogeno, hydroxy, cyano, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, carbamoyl,

- 5 N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N -(1-6C)alkylcarbamoyl-(1-6C)alkyl and N,N -di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl; and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings

10 defined herein;

(asss) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen,

G^4 is selected from hydrogen, fluoro, chloro, methyl and ethynyl, and

G^3 is a group of the formula:

15 $-X^{11}-Q^{10}$

wherein X^{11} is O and Q^{10} is benzyl which is optionally substituted by 1 or 2 substituents, which may be the same or different, selected from halogeno, cyano and (1-4C)alkyl; and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;

20 (tttt) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen,

G^4 is selected from hydrogen, chloro, methyl and ethynyl, and

G^3 is a group of the formula:

$-X^{11}-Q^{10}$

25 wherein X^{11} is O and Q^{10} is benzyl which is optionally substituted by 1 substituent selected from fluoro and cyano (for example Q^{10} is benzyl or 3-fluorobenzyl); and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;

(uuuu) Q^2 is a group of formula Ia wherein:

30 G^1 , G^2 and G^5 are hydrogen,

G^4 is selected from hydrogen, chloro, methyl and ethynyl, and

G^3 is a group of the formula:

$-X^{11}-Q^{10}$

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wherein X^{11} is O and Q^{10} is selected from furfuryl, 3-furylmethyl, 2- or 3-thienylmethyl, 2-, 4- or 5-oxazolymethyl, 3-, 4- or 5-isoxazolymethyl, 2-, 4- or 5-1H-imidazolymethyl, 2-, 4- or 5-thiazolymethyl, 3- or 5-(1H-1,2,4-triazolyl)methyl, 3- or 4-(1,2,5-thiadiazolyl)methyl, 2-, 3- or 4-pyridylmethyl and 2-, 4- or 5-pyrimidinylmethyl, and wherein heteroaryl group within

5 Q^{10} optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings defined herein;

10 (vvvv) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen,

G^4 is selected from hydrogen, chloro, methyl and ethynyl, and

G^3 is a group of the formula:



15 wherein X^{11} is O and Q^{10} is selected from isoxazolymethyl, thiazolymethyl and pyridylmethyl, and wherein heteroaryl group within Q^{10} optionally bears 1 or 2 substituents, which may be the same or different, selected from hydroxy, amino, methyl, methylamino and di-methylamino;

and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings

20 defined herein; and

(www) Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen,

G^4 is selected from chloro and methyl, and

G^3 is a group of the formula:

25 $-X^{11}-Q^{10}$

wherein X^{11} is O and Q^{10} is selected from 3-isoxazolymethyl and 4-thiazolymethyl, and wherein heteroaryl group within Q^{10} optionally bears 1 substituent selected from methyl and ethyl (for example Q^{10} is 5-methyl-isoxazol-3-ylmethyl, or 4-thiazolyl);

and wherein m is 1, R^1 is located at the 7-position and wherein R^1 has any of the meanings

30 defined herein.

A particular embodiment of the present invention is a quinazoline derivative of the Formula I wherein:

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m is 0 or m is 1 and the R¹ group, when present, is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, pentyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, propylmethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido, 5 propiolamido, pyrrolidin-1-yl, piperidino, homopiperidin-1-yl, morpholino, thiamorpholino, piperazin-1-yl and homopiperazin-1-yl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(CH₃), CO, CONH and NHCO,

10 and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, and dimethylamino, or from a group of the formula:



wherein X³ is a direct bond or is selected from O, NH and N(CH₃) and Q⁵ is selected from 15 pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, homopiperidin-1-yl, piperazin-1-yl homopiperazin-1-yl, phenyl, 2-, 3- or 4-pyridyl and 2-, 4- or 5-pyrimidinyl,

and wherein any phenyl, pyridyl, pyrimidinyl or heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, 20 selected from fluoro, chloro, trifluoromethyl, hydroxy, methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy, 2-methoxyethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 3-methoxypropoxy, aminomethoxy, 2-aminoethoxy, 3-aminopropoxy, methylaminomethoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, dimethylaminomethoxy, 2-dimethylaminoethoxy, amino, methylamino, dimethylamino, and wherein any pyrrolidinyl, piperidinyl, piperazinyl, 25 homopiperidinyl or homopiperazinyl moiety within R¹ is optionally further substituted on an available nitrogen atom with a substituent selected from tetrahydrofurfuryl, tetrahydrofuran-3-ylmethyl, 1-methylpiperidin-4-yl 1-ethylpiperidin-4-yl, 1-methylpiperidin-3-yl 1-ethylpiperidin-3-yl and 2-morpholinoethyl, and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 30 substituents;

the Q¹-Z- group is selected from cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-3-yloxy, 1-oxotetrahydrothiopyran-3-yloxy,

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- 1,1-dioxotetrahydrothiopyran-3-yloxy, tetrahydrothiopyran-4-yloxy,
 1-oxotetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy,
 tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy,
 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy,
 5 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy,
 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy,
 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-
 4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy,
 10 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy,
 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, homopiperidin-3-yloxy,
 homopiperidin-4-yloxy, homopiperidin-3-ylmethoxy, 2-piperazin-1-ylethoxy,
 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

- and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each
 15 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
 methylsulphonyl, methylamino and dimethylamino,

and wherein any phenyl or heterocyclyl group within the Q¹-Z- group optionally bears
 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,
 trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,

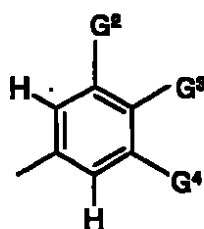
- 20 and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo
 substituents;

R³ is hydrogen;

L is a direct bond; and

Q² is an aryl group of formula Ib

25



Ib

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wherein each of G^2 , G^3 and G^4 , which may be the same or different, is selected from hydrogen, fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl and ethynyl, provided that at least one of G^2 , G^3 and G^4 is other than hydrogen,

or G^3 and G^4 together form a group of formula : -CH=CH-NH-, -NH-CH=CH-,

- 5 -NH-N=CH- or -CH=N-NH-, -S-N=CH- or -CH=N-S-, and the 9-membered bicyclic heteroaryl ring so formed optionally bears on the heteroaryl portion of the bicyclic ring 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl and ethyl;
or a pharmaceutically-acceptable acid-addition salt thereof.

- 10 A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 0 or 1 and the R^1 group, when present, is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, pyrrolidin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy,

- 15 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy,

3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy

- and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R^1 substituent
20 are optionally separated by the insertion into the chain of a group selected from O, NH and $N(CH_3)$,

and wherein any terminal CH_3 group within a (1-6C)alkoxy chain in a R^1 substituent optionally bears on said terminal CH_3 group a substituent selected from hydroxy, amino and N -(1-methylpyrrolidin-3-yl)- N -methyldamino,

- 25 and wherein any pyrrolidinyl or piperidinyl group within a R^1 substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,

and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl, 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl;

- 30 the Q^1 -Z- group is selected from cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxodotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy,

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pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy and azetidin-3-yloxy,

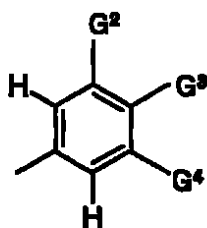
- and wherein the azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within the Q¹-Z- group is optionally N- substituted by a substituent selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, allyl, 2-propynyl, acetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, acetylmethyl, 2-acetylethyl, methoxycarbonylmethyl and 2-methoxycarbonylethyl,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

R³ is hydrogen;

L is a direct bond; and

- Q² is an aryl group of formula Ib



Ib

- wherein G² is hydrogen, and G³ and G⁴, which may be the same or different, is selected from hydrogen, fluoro, chloro, bromo, cyano, hydroxy, methyl, ethyl, and ethynyl, provided that at least one of G³ and G⁴ is other than hydrogen,

- or G³ and G⁴ together form a group of formula :- -CH=CH-NH-, -NH-CH=CH-, -NH-N=CH-, -CH=N-NH-, and the 9-membered bicyclic heteroaryl ring so formed optionally bears on the heteroaryl portion of the bicyclic ring 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, and methyl;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

- m is 0 or 1 and the R^1 group, when present, is located at the 7-position and is selected from methoxy, 2-methoxyethoxy, 3-(R)-dimethylaminopyrrolidin-1-yl, ,
 1-methylpiperidin-4-ylmethoxy, 3-(N-(2-hydroxyethyl)-N-methylamino)propoxy, 2-(N-(2-methoxyethyl)-N-methylamino)ethoxy, 2-(N-(2-hydroxyethyl)-N-methylamino)ethoxy,
 5 3-(N-(2-dimethylaminoethyl)-N-methylamino)propoxy, 2-(N-(2-dimethylaminoethyl)-N-methylamino)ethoxy, 3-pyrrolidin-1-ylpropoxy, 3-(3-hydroxypyrrolidin-1-yl)propoxy, 2-pyrrolidin-1-ylethoxy, 2-(3-hydroxypyrrolidin-1-yl)ethoxy, 2-(3-dimethylaminopyrrolidin-1-yl)ethoxy, 3-(3-dimethylaminopyrrolidin-1-yl)propoxy, 3-(N-methyl-N-(1-methylpyrrolidin-3-yl)amino)propoxy, 2-(N-methyl-N-
 10 (1-methylpyrrolidin-3-yl)amino)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-homopiperidinoethoxy, 3-homopiperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-isopropylpiperazin-1-yl)propoxy, 2-(4-isopropylpiperazin-1-yl)ethoxy, 3-(4-(2-methoxyethyl)piperazin-1-yl)propoxy, 2-(4-(2-methoxyethyl)piperazin-1-yl)ethoxy,
 15 2-(4-(2-morpholinoethyl)piperazin-1-yl)ethoxy, 3-(4-(2-morpholinoethyl)piperazin-1-yl)propoxy, 2-(4-tetrahydrofurfuryl)piperazin-1-ylethoxy, 3-(4-tetrahydrofurfuryl)piperazin-1-ylpropoxy, 2-(4-(1-methylpiperidin-4-yl)piperazin-1-ylethoxy,
 20 3-(4-(1-methylpiperidin-4-yl)piperazin-1-ylpropoxy, 2-(4-methylhomopiperazin-1-yl)ethoxy, 3-(4-methylhomopiperazin-1-yl)propoxy, the Q^1 -Z- group is selected from cyclopentyloxy, 1-methylazetidin-3-yloxy, 1-isopropylazetidin-3-yloxy, tetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, tetrahydrofuran-3-yloxy,
 25 1-methylpyrrolidin-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 1-ethylpiperidin-4-yloxy, 1-propylpiperidin-4-yloxy, 1-(2-methoxyethyl)piperidin-4-yloxy, 1-acetyl piperidin-4-yloxy, 1-acetylmethylpiperidin-4-yloxy, 1-allylpiperidin-4-yloxy, 1-(2-propynyl)piperidin-4-yloxy,
 30 1-methoxycarbonylmethylpiperidin-4-yloxy, 1-carbamoylmethylpiperidin-4-yloxy and 1-methanesulphonylpiperidin-4-yloxy;

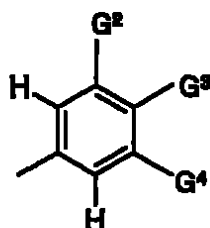
R^3 is hydrogen;

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L is a direct bond or CH(CH₃); and

Q² is an aryl group of formula Ib



Ib

5

wherein G² is hydrogen, and G³ and G⁴, which may be the same or different, is selected from hydrogen, fluoro, chloro, bromo, hydroxy, methyl and ethynyl, provided that when L is a direct bond at least one of G³ and G⁴ is other than hydrogen,

or G³ and G⁴ together form a group of formula :- -CH=CH-NH-, -NH-CH=CH-, -NH-N=CH-,

- 10 -CH=N-NH-, -S-N=CH- or -CH=N-S- and the 9-membered bicyclic heteroaryl ring so formed optionally bears on a carbon atom in the heteroaryl portion of the bicyclic ring 1 substituent selected from fluoro, chloro, bromo, cyano, and methyl;
or a pharmaceutically-acceptable acid-addition salt thereof.

Suitable groups of the formula 1b in this embodiment include, for example,

- 15 3-bromophenyl, 3-chlorophenyl, 3-fluorophenyl, 3-methylphenyl, 3-ethynylphenyl, 3-chloro-4-hydroxyphenyl, 3-chloro-4-fluorophenyl, indol-5-yl, 3-bromoindol-5-yl, 3-chloroindol-5-yl, 3-cyanoindol-5-yl, 3-methylindol-5-yl, 3-chloroindol-5-yl indazol-5-yl, 3-bromoindazol-5-yl, 3-chloroindazol-5-yl, benzisothiazol-5-yl and 3-methyl-benzisothiazol-5-yl;

- 20 or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein m is 0 or m is 1 and the R¹ group, when present, is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, pentyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, N-propyl-N-methylamino,

- 25 N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido, propiolamido, pyrrolidin-1-yl, piperidino, homopiperidin-1-yl, morpholino, thiomorpholino, piperazin-1-yl and homopiperazin-1-yl,

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and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(CH₃), CO, CONH and NHCO,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
5 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, and dimethylamino, or from a group of the formula:



wherein X³ is a direct bond or is selected from O, NH and N(CH₃) and Q⁵ is selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-3-yl,
10 piperidin-4-yl, homopiperidin-1-yl, piperazin-1-yl homopiperazin-1-yl, phenyl, (2-, 3- or 4-)pyridyl and (2-, 4- or 5-)pyrimidinyl,

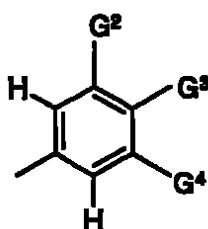
and wherein any phenyl, pyridyl, pyrimidinyl or heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, methyl, ethyl, n-propyl, isopropyl,
15 methoxy, ethoxy, 2-methoxyethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 3-methoxypropoxy, aminomethoxy, 2-aminoethoxy, 3-aminopropoxy, methylaminomethoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, dimethylaminomethoxy, 2-dimethylaminoethoxy, amino, methylamino, dimethylamino, and wherein any pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl or homopiperazinyl moiety within R¹ is optionally further substituted on an
20 available nitrogen atom with a substituent selected from tetrahydrofurfuryl, tetrahydrofuran-3-ylmethyl, 1-methylpiperidin-4-yl 1-ethylpiperidin-4-yl, 1-methylpiperidin-3-yl 1-ethylpiperidin-3-yl and 2-morpholinoethyl, and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo substituents;

25 the Q¹-Z- group is selected from cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-3-yloxy, 1-oxotetrahydrothiopyran-3-yloxy, 1,1-dioxotetrahydrothiopyran-3-yloxy, tetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy,
30 tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy,

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- 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy,
- 5 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy, homopiperidin-3-ylmethoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,
- and wherein any CH_2 or CH_3 group within the $\text{Q}^1\text{-Z-}$ group optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy,
- 10 methylsulphonyl, methylamino and dimethylamino,
- and wherein any phenyl or heterocyclyl group within the $\text{Q}^1\text{-Z-}$ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,
- and wherein any heterocyclyl group within the $\text{Q}^1\text{-Z-}$ group optionally bears 1 or 2 oxo
- 15 substituents;
- R^3 is hydrogen;
- L is a direct bond; and
- Q^2 is an aryl group of formula Ib



Ib

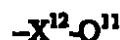
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wherein G^3 and G^4 together form a group of formula:- $-\text{CH}=\text{CH}-\text{NH}-$, $-\text{NH}-\text{CH}=\text{CH}-$, $-\text{NH}-\text{N}=\text{CH}-$ or $-\text{CH}=\text{N}-\text{NH}-$,

- 25 and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 are linked together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group selected from trifluoromethyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl,

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(1-4C)alkoxycarbonyl, carbamoyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl and (1-4C)alkylsulphonyl, or from a group of the formula:



wherein X^{12} is a direct bond or is selected from SO_2 and CO, wherein R^{21} is hydrogen or (1-6C)alkyl and Q^{11} is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, which optionally bears 1 or 2 substituents, which may be the same or different, selected from cyano, halogeno, hydroxy, (1-6C)alkyl and (1-6C)alkoxy,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 together are linked optionally bears on an available carbon atom in the heteroaryl portion of the bicyclic ring 1 substituent selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and any bicyclic heteroaryl ring so formed optionally bears 1 or 2 oxo or thioxo groups,

and G^2 is selected from hydrogen, halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino; or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 0 or 1 and the R^1 group, when present, is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, pyrrolidin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy, 3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy

and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH and $N(CH_3)$,

and wherein any terminal CH_3 group within a (1-6C)alkoxy chain in a R^1 substituent optionally bears on the terminal CH_3 group a substituent selected from hydroxy, amino and N-(1-methylpyrrolidin-3-yl)-N-methylamino,

and wherein any pyrrolidinyl or piperidinyl group within a R^1 substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,

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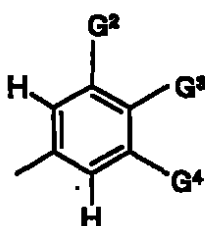
and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl, 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl;

the Q^1 -Z- group is selected from cyclopentyloxy, tetrahydrofuran-3-yloxy, 5 tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxodotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy and azetidin-3-yloxy,

10 and wherein the azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within the Q^1 -Z- group is optionally N- substituted by a substituent selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, allyl, 2-propynyl, acetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, 15 N,N-dimethylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, acetylmethyl, 2-acetylethyl, methoxycarbonylmethyl and 2-methoxycarbonylethyl,

and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1 or 2 oxo substituents;

20 R^3 is hydrogen;
L is a direct bond; and
 Q^2 is an aryl group of formula Ib

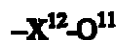


Ib

25 wherein G^3 and G^4 together form a group of formula:- $-CH=CH-NH-$, $-NH-CH=CH-$, $-NH-N=CH-$ or $-CH=N-NH-$,

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and the 9-membered bicyclic heteroaryl ring formed when G³ and G⁴ are linked together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group of the formula:



- 5 wherein X¹² is a direct bond or is selected from SO₂ and CO, wherein Q¹¹ is phenyl, benzyl, 2-phenylethyl, 2-furyl, furfuryl, 3-furyl, 3-furylmethyl, 2-oxazolyl, 4-oxazolyl, 2-oxazolylmethyl, 4-oxazolylmethyl, 2-imidazolyl, 4-imidazolyl, 2-imidazolylmethyl, 4-imidazolylmethyl, 2-, 3- or 4-pyridyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 2-, 4- or 5-pyrimidinyl, 2-, 4- or 5-pyrimidinylmethyl, 2-(2-, 4- or 5-pyrimidinyl)ethyl, 10 1,2,4-triazol-3-yl, 1,2,4-triazol-5-ylmethyl, triazol-3-ylmethyl, 1,2,4-triazol-5-yl, 2-thienyl, 3-thienyl, 2-thienylmethyl, 3-thienylmethyl, 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl, 2-thiazolyl, 4-thiazolyl, 2-thiazolylmethyl, 4-thiazolylmethyl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-3-ylmethyl, 2-(1,2,5-thiadiazol-3-yl)ethyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, 15 hydroxy, methyl and ethyl,

and the 9-membered bicyclic heteroaryl ring formed when G³ and G⁴ together are linked optionally bears on an available carbon atom in the heteroaryl portion of the bicyclic ring 1 substituent selected from fluoro, chloro, bromo, cyano, hydroxy, amino, methyl, ethyl, vinyl, ethynyl, methylamino and di-methylamino,

- 20 and G² is selected from hydrogen, fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl, vinyl, ethynyl, methylamino and dimethylamino; or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein m is 0 or 1 and the R¹ group, when present, is located at the 7-position and is 25 methoxy,

Q¹-Z- is 1-methylpiperidin-1-yloxy,

R³ is hydrogen;

L is a direct bond; and

Q³ is an aryl group of formula Ib as hereinbefore defined wherein,

- 30 G² is hydrogen,

and G³ and G⁴ together form a group of formula: -NH-CH=CH- or -NH-N=CH-,

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and the 9-membered bicyclic heteroaryl ring formed when G³ and G⁴ are linked together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group of the formula:



5 wherein X¹² is a direct bond or is SO₂, and Q¹¹ is phenyl, benzyl, or 2-pyridylmethyl which optionally bears a fluoro substituent,

and the 9-membered bicyclic heteroaryl ring formed when G³ and G⁴ together are linked optionally bears at the 3-position a chloro substituent;
or a pharmaceutically acceptable salt thereof.

10 Suitable values for Q² in this embodiment include, for example

1-benzenesulphonylindol-5-yl, 1-benzylindol-5-yl, 1-(2-pyridylmethyl)indol-5-yl,
1-(2-pyridylmethyl)indazol-5-yl and 1-(3-fluorobenzyl)indazol-5-yl.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein m is 0 or m is 1 and the R¹ group, when present, is selected from hydroxy, amino,
15 methyl, ethyl, propyl, butyl, pentyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, propylmethylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido, propiolamido, pyrrolidin-1-yl, piperidino, homopiperidin-1-yl, morpholino, thiamorpholino, piperazin-1-yl and homopiperazin-1-yl,

20 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(CH₃), CO, CONH and NHCO,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
25 methylsulphonyl, methylamino, and dimethylamino, or from a group of the formula:



wherein X³ is a direct bond or is selected from O, NH and N(CH₃) and Q⁵ is selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, homopiperidin-1-yl, piperazin-1-yl homopiperazin-1-yl, phenyl, 2-, 3- or
30 4-pyridyl and 2-, 4- or 5-pyrimidinyl,

and wherein any phenyl, pyridyl, pyrimidinyl or heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, methyl, ethyl, n-propyl, isopropyl,

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methoxy, ethoxy, 2-methoxyethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 3-methoxypropoxy, aminomethoxy, 2-aminoethoxy, 3-aminopropoxy, methylaminomethoxy, 2-methylaminomethoxy, 2-ethylaminomethoxy, dimethylaminomethoxy, 2-dimethylaminomethoxy, amino, methylamino, dimethylamino, and wherein any pyrrolidinyl, piperidinyl, piperazinyl, 5 homopiperidinyl or homopiperazinyl moiety within R¹ is optionally further substituted on an available nitrogen atom with a substituent selected from tetrahydrofurfuryl, tetrahydrofuran-3-ylmethyl, 1-methylpiperidin-4-yl 1-ethylpiperidin-4-yl, 1-methylpiperidin-3-yl 1-ethylpiperidin-3-yl and 2-morpholinoethyl, and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo
10 substituents;

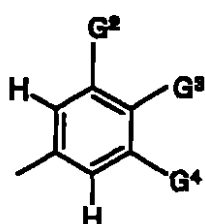
the Q¹-Z- group is selected from cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-3-yloxy, 1-oxotetrahydrothiopyran-3-yloxy, 1,1-dioxotetrahydrothiopyran-3-yloxy, tetrahydrothiopyran-4-yloxy, 15 1-oxotetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 20 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, homopiperidin-3-yloxy, 25 homopiperidin-4-yloxy, homopiperidin-3-ylmethoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy, and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino and dimethylamino, 30 and wherein any phenyl or heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

R³ is hydrogen;

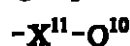
L is a direct bond; and

5 Q² is an aryl group of formula Ib



Ib

10 wherein G³ is selected from carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, or from a group of the formula :



wherein X¹¹ is CON(R²⁰), wherein R²⁰ is hydrogen or (1-6C)alkyl, and Q¹⁰ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl,

15 (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein Q¹⁰ optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, cyano, nitro, hydroxy, amino, carbamoyl, methyl, ethyl, vinyl, allyl, ethynyl, methoxy, ethoxy, methylthio, ethylthio,

20 methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl, methylamino, di-methylamino, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl,

N,N-dimethylcarbamoyl, acetyl, propionyl, acetamido, propionamido, N-methylsulphamoyl,

N,N-dimethylsulphamoyl, methanesulphonylamino and N-methyl-methanesulphonylamino,

and wherein any heterocyclyl group within Q¹⁰ optionally bears 1 or 2 oxo or thioxo

25 substituents,

and G² and G⁴ each independently is selected from hydrogen, fluoro, chloro, trifluoromethyl, cyano, nitro, hydroxy, amino, methyl, ethyl, vinyl, allyl, ethynyl;

or a pharmaceutically acceptable salt thereof.

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A further embodiment of the invention is a quinazoline derivative of the Formula I wherein m is 0 or m is 1 and the R^1 group, when present, is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, pentyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, propylmethylamino,

- 5 N -methylcarbamoyl, N,N -dimethylcarbamoyl, acetamido, propionamido, acrylamido, propiolamido, pyrrolidin-1-yl, piperidino, homopiperidin-1-yl, morpholino, thiamorpholino, piperazin-1-yl and homopiperazin-1-yl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O,
10 NH, $N(CH_3)$, CO, CONH and NHCO,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, and dimethylamino, or from a group of the formula:



- 15 wherein X^3 is a direct bond or is selected from O, NH and $N(CH_3)$ and Q^5 is selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, homopiperidin-1-yl, piperazin-1-yl homopiperazin-1-yl, phenyl, 2-, 3- or 4-pyridyl and 2-, 4- or 5-pyrimidinyl,

and wherein any phenyl, pyridyl, pyrimidinyl or heterocyclyl group within a
20 substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, methyl, ethyl, n -propyl, isopropyl, methoxy, ethoxy, 2-methoxyethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 3-methoxypropoxy, aminomethoxy, 2-aminoethoxy, 3-aminopropoxy, methylaminomethoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, dimethylaminomethoxy, 2-dimethylaminoethoxy,
25 amino, methylamino, dimethylamino, and wherein any pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl or homopiperazinyl moiety within R^1 is optionally further substituted on an available nitrogen atom with a substituent selected from tetrahydrofurfuryl, tetrahydrofuran-3-ylmethyl, 1-methylpiperidin-4-yl 1-ethylpiperidin-4-yl, 1-methylpiperidin-3-yl 1-ethylpiperidin-3-yl and 2-morpholinoethyl,

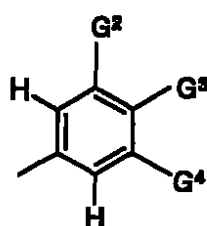
- 30 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

the Q^1-Z group is selected from cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy,

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100

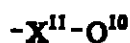
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- tetrahydropyran-4-yloxy, tetrahydrothiopyran-3-yloxy, 1-oxotetrahydrothiopyran-3-yloxy,
 1,1-dioxotetrahydrothiopyran-3-yloxy, tetrahydrothiopyran-4-yloxy,
 1-oxotetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy,
 tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy,
 5 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy,
 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy,
 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy,
 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-
 4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,
 10 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy,
 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy,
 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, homopiperidin-3-yloxy,
 homopiperidin-4-yloxy, homopiperidin-3-ylmethoxy, 2-piperazin-1-ylethoxy,
 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,
 15 and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each
 said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
 methylsulphonyl, methylamino and dimethylamino,
 and wherein any phenyl or heterocyclyl group within the Q¹-Z- group optionally bears
 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,
 20 trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy,
 and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo
 substituents;
- R³ is hydrogen;
 L is a direct bond; and
 25 Q² is an aryl group of formula Ib



Ib

wherein G^3 is selected from a group of the formula:



wherein X^{11} is CO and Q^{10} is a 5 to 10 membered nitrogen containing heterocyclic group

5 linked to X^{11} by a nitrogen atom,

and Q^{10} optionally bears 1 or 2 substituents selected from halogeno, cyano, hydroxy,

amino, (1-6C)alkyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and G^2 and G^4 each independently is selected from hydrogen, halogeno, trifluoromethyl,

cyano, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino and

10 di-[(1-6C)alkyl]amino;

or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I

wherein m is 0 or 1 and the R^1 group, when present, is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy,

15 pyrrolidin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy,

3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy,

3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,

2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy,

3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy

20 and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH and $N(CH_3)$,

and wherein any terminal CH_3 group within a (1-6C)alkoxy chain in a R^1 substituent optionally bears on the terminal CH_3 group a substituent selected from hydroxy, amino and

25 1-methylpyrrolidin-3-yl(methyl)amino,

and wherein any pyrrolidinyl or piperidinyl group within a R^1 substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,

and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent

optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl,

30 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl;

the Q^1-Z group is selected from cyclopentyloxy, tetrahydrofuran-3-yloxy,

tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy,

1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy,

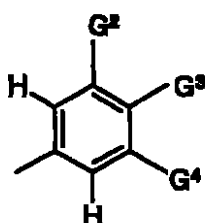
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1,1-dioxodotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy and azetidin-3-yloxy,

- and wherein the azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within
- 5 the Q¹-Z- group is optionally N- substituted by a substituent selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, ~~tert~~-butyl, allyl, 2-propynyl, acetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, ~~tert~~-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl,
- 10 2-(N,N-dimethylcarbamoyl)ethyl, acetylmethyl, 2-acetylethyl, methoxycarbonylmethyl and 2-methoxycarbonylethyl,

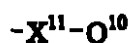
and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

- R³ is hydrogen;
- 15 L is a direct bond; and
- Q² is an aryl group of formula Ib



Ib

- 20 wherein G³ is selected from a group of the formula:



wherein X¹¹ is CO and Q¹⁰ is selected from pyrrolidin-1-yl, piperidino, homopiperidino, morpholino, piperazin-1-yl, homopiperazin-1-yl, decahydroquinolin-1-yl and decahydroisoquinolin-2-yl,

- 25 and wherein Q¹⁰ optionally bears 1 or 2 substituents selected from fluoro, chloro, bromo, cyano, hydroxy, amino, methyl, ethyl, methylamino and dimethylamino,

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and G^2 and G^4 each independently is selected from hydrogen, fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, amino, methyl, ethyl, vinyl, ethynyl, methylamino and di-methylamino;

or a pharmaceutically acceptable salt thereof.

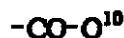
- 5 A further embodiment of the invention is a quinazoline derivative of the Formula I wherein m is 0 or 1 and the R^1 group, when present, is located at the 7-position and is methoxy,

the Q^1 -Z- group is 1-methylpiperidin-4-yl,

R^3 is hydrogen;

- 10 L is a direct bond; and

Q^3 is an aryl group of formula Ib as hereinbefore defined wherein wherein G^3 is a group of the formula:



- wherein Q^{10} is selected from piperidino, homopiperidino, decahydroquinolin-1-yl and
15 decahydroisoquinolin-2-yl, which is optionally substituted by methyl,

and G^2 and G^4 each independently is selected from hydrogen, chloro and ethynyl, or a pharmaceutically acceptable salt thereof.

Suitable values for Q^2 in this embodiment include for example

- 3-chloro-4-(homopiperidin-1-ylcarbonyl)phenyl,
20 3-chloro-4-(decahydroquinolin-1-ylcarbonyl)phenyl,
3-chloro-4-(decahydroisoquinolin-1-ylcarbonyl)phenyl,
3-chloro-4-(3-methylpiperidin-1-ylcarbonyl)phenyl,
3-chloro-4-(4-methylpiperidin-1-ylcarbonyl)phenyl,
3-ethynyl-4-(decahydroquinolin-1-ylcarbonyl)phenyl and
25 3-ethynyl-4-(decahydroquinolin-1-ylcarbonyl)phenyl.

- A further embodiment of the invention is a quinazoline derivative of the Formula I wherein m is 0 or m is 1 and the R^1 group, when present, is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, pentyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, propylmethylamino,
30 N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido, propiolamido, pyrrolidin-1-yl, piperidino, homopiperidin-1-yl, morpholino, thiamorpholino, piperazin-1-yl and homopiperazin-1-yl,

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and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(CH₃), CO, CONH and NHCO,

and wherein any CH₂ or CH₃ group within a R^1 substituent optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy, methylsulphonyl, methylamino, and dimethylamino, or from a group of the formula:



wherein X^3 is a direct bond or is selected from O, NH and N(CH₃) and Q^5 is selected from pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, homopiperidin-1-yl, piperazin-1-yl homopiperazin-1-yl, phenyl, 2-, 3- or 4-pyridyl and 2-, 4- or 5-pyrimidinyl,

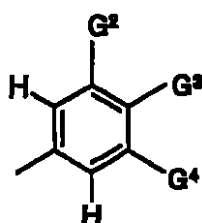
and wherein any phenyl, pyridyl, pyrimidinyl or heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, methyl, ethyl, n-propyl, isopropyl, methoxy, ethoxy, 2-methoxyethoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 3-methoxypropoxy, aminomethoxy, 2-aminoethoxy, 3-aminopropoxy, methylaminomethoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, dimethylaminomethoxy, 2-dimethylaminoethoxy, amino, methylamino, dimethylamino, and wherein any pyrrolidinyl, piperidinyl, piperazinyl, homopiperidinyl or homopiperazinyl moiety within R^1 is optionally further substituted on an available nitrogen atom with a substituent selected from tetrahydrofurfuryl, tetrahydrofuran-3-ylmethyl, 1-methylpiperidin-4-yl 1-ethylpiperidin-4-yl, 1-methylpiperidin-3-yl, 1-ethylpiperidin-3-yl and 2-morpholinoethyl, and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo substituents;

the Q^1-Z group is selected from cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-3-yloxy, 1-oxotetrahydrothiopyran-3-yloxy, 1,1-dioxotetrahydrothiopyran-3-yloxy, tetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, 2-imidazol-1-ylethoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy,

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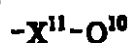
- 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy,
- 5 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy, homopiperidin-3-ylmethoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy, and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each said CH₂ or CH₃ group a substituent selected from hydroxy, amino, methoxy,
- 10 methylsulphonyl, methylamino and dimethylamino, and wherein any phenyl or heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl and methoxy, and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo
- 15 substituents;
- R³ is hydrogen;
- L is a direct bond; and
- Q² is an aryl group of formula Ib



Ib

20

wherein G³ is selected from a group of the formula:



- wherein X¹¹ is a direct bond or is selected from O, S, SO₂, N(R²⁰), CO, CH(OR²⁰), C(R²⁰)₂O, C(R²⁰)₂NR²⁰, and C(R²⁰)₂S, wherein R²⁰ is hydrogen, methyl or ethyl, and Q¹⁰ is a phenyl, benzyl, 2-phenylethyl, naphthyl, naphthylmethyl or 2-naphthylethyl group which is optionally substituted with 1 or 2 substituents selected from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl, isopropyl, vinyl, ethynyl and cyano,
- 25

- or Q¹⁰ is a heteroaryl moiety selected from furyl, furylmethyl, 2-(furyl)ethyl, thienyl, thienylmethyl, 2-(thienyl)ethyl, oxazolyl, oxazolymethyl, 2-(oxazolyl)ethyl, isoxazolyl, isoxazolymethyl, 2-(isoxazolyl)ethyl, imidazolyl, imidazolymethyl, 2-(imidazolyl)ethyl, thiazolyl, thiazolymethyl, 2-(thiazolyl)ethyl, 1,2,4-triazolyl, 1,2,4-triazolymethyl, 2-(1,2,4-triazolyl)ethyl, 1,2,5-thiadiazolyl, 1,2,5-thiadiazolymethyl, 2-(1,2,5-thiadiazolyl)ethyl, pyridyl, pyridylmethyl, 2-(pyridyl)ethyl, pyrimidinyl, pyrimidinylmethyl, 2-(pyrimidinyl)ethyl, 1,3-benzodioxolyl, 1,3-benzodioxolymethyl, 2-(1,3-benzodioxolyl)ethyl, quinoliny, quinolinylmethyl, 2-(quinoliny)ethyl, isoquinoliny, isoquinolinylmethyl, 2-(isoquinoliny)ethyl, quinazoliny, quinazolinylmethyl and 2-(quinazoliny)ethyl, which is optionally substituted with one or two substituents selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, ethyl, isopropyl, methoxy and ethoxy,
- and each of G² and G⁴ independently is selected from hydrogen, fluoro, chloro, bromo, trifluoromethyl, methyl, ethyl, vinyl, allyl, ethynyl, methylamino and di-methylamino;
- or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

- m is 0 or 1 and the R¹ group, when present, is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, pyrrolidin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy, 3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy
- and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH and N(CH₃),

- and wherein any terminal CH₃ group within a (1-6C)alkoxy chain in a R¹ substituent optionally bears on the terminal CH₃ group a substituent selected from hydroxy, amino and N-(1-methylpyrrolidin-3-yl)-N-methylamino,

and wherein any pyrrolidinyl or piperidinyl group within a R¹ substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,

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and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl, 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl;

the Q^1 -Z- group is selected from cyclopentyloxy, tetrahydrofuran-3-yloxy, 5 tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxodotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy and azetidin-3-yloxy,

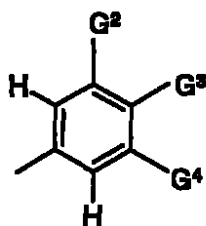
10 and wherein the azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within the Q^1 -Z- group is optionally N- substituted by a substituent selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, allyl, 2-propynyl, acetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, 15 N,N-di-methylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-di-methylcarbamoyl)ethyl, acetylmethyl, 2-acetylethyl, methoxycarbonylmethyl and 2-methoxycarbonylethyl,

and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1 or 2 oxo substituents;

20 R^3 is hydrogen;

L is a direct bond; and

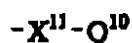
Q^2 is an aryl group of formula Ib

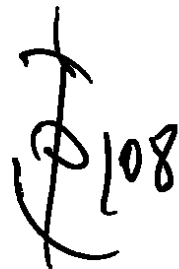


Ib

25

wherein G^3 is a group of the formula:





- wherein X^{11} is a direct bond or is selected from O, S, $N(R^{20})$, CO, $CH(OR^{20})$ and $C(R^{20})_2NR^{20}$, wherein R^{20} is hydrogen or methyl, and Q^{10} is a phenyl or benzyl group which is optionally substituted with 1 or 2 substituents selected from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl, isopropyl, ethynyl and cyano,
- 5 or Q^{10} is a heteroaryl moiety selected from 2-1H-imidazolyl, 2-1H-imidazolylmethyl, 4-thiazolylmethyl, 2-thienylmethyl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-3-ylmethyl, 3-isoxazolylmethyl, 2-, 3- or 4-pyridyl, 2-, 3- or 4-pyridylmethyl, 8-quinoliny, and 8-quinolylmethyl, which heteroaryl moiety is optionally substituted with one or two substituents selected from fluoro, chloro, bromo, trifluoromethyl, methyl, ethynyl and cyano;
- 10 and each of G^2 and G^4 independently is selected from hydrogen, fluoro, chloro, bromo, methyl, and ethynyl;
- or a pharmaceutically acceptable salt thereof.

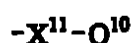
A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

- 15 m is 0 or 1 and the R^1 group, when present, is located at the 7-position and is selected from methoxy and 3-(R)-dimethylaminopyrrolidin-1-yl,
- the Q^1 -Z- group is selected from piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 1-propylpiperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 1-allylpiperidin-4-yloxy, 1-(2-propyny)piperidin-4-yloxy, 1-(2-methoxyethyl)piperidin-4-yloxy,
- 20 1-acetylmethylpiperidin-4-yloxy, 1-tert-butoxycarbonylpiperidin-4-yloxy, 1-methoxycarbonylmethylpiperidin-4-yloxy, 1-methanesulphonylpiperidin-4-yloxy and 1-carbamoylmethylpiperidin-4-yloxy;

R^3 is hydrogen;

L is a direct bond; and

- 25 Q^2 is an aryl group of formula Ib as hereinbefore defined wherein G^2 is selected from a group of the formula:



- wherein X^{11} is selected from O, S, NH, $N(CH_3)$, CO and CH_2NH , and Q^{10} is selected from phenyl or benzyl, 2-thienyl, 2-thienylmethyl, 2-1H-imidazolyl, 2-1H-imidazolylmethyl, 3-isoxazolylmethyl, 4-thiazolyl, 3-(1,2,5-thiadiazolyl), 2-pyridyl, 2-pyridylmethyl, 3-pyridyl, 3-pyridylmethyl, 4-pyridyl, 4-pyridylmethyl and 8-quinoliny, which is optionally substituted by
- 30 1 or 2 substituents selected from fluoro, chloro, methyl, nitro and cyano,

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and each of G² and G⁴ independently is selected from hydrogen and chloro;
or a pharmaceutically acceptable salt thereof.

Suitable values for G³ in this embodiment include, for example phenoxy, 3-fluorophenoxy, 2,3-difluorophenoxy, phenylthio, 2-fluorobenzoyloxy, 2-chlorobenzoyloxy, 2-cyanobenzoyloxy, 3-fluorobenzoyloxy, 3-fluorobenzoyloxy, 3-methylbenzoyloxy, 4-fluorobenzoyloxy, 2-methoxybenzoyloxy, 2,6-difluorobenzoyloxy, 2,6-dichlorobenzoyloxy, 2, 5-dimethylbenzoyloxy, 4-methyl-2-nitrobenzoyloxy, 3-fluorophenylaminomethyl, 5-chloro-2-thienyl, 2-thienylcarbonyl, 1-methyl-2-1H-imidazolyl, 1-methyl-2-1H-imidazolylmethoxy, 5-methyl-3-isoxazolylmethoxy, 2-methyl-4-thiazolylmethoxy, 1,2,5-thiadiazol-3-ylmethoxy, 2-pyridyl, 3-pyridyl, 2-pyridylmethoxy, 3-pyridylmethoxy, 4-pyridylmethoxy, 6-chloro-3-pyridylmethoxy, N-(2-pyridylmethyl)amino, N-(2-pyridyl)-N-(methyl)amino, N-(2-pyridylmethyl)-N-methylamino, 2-pyrimidinyl and 8-quinolinyloxy.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 0 or 1 and the R¹ group, when present, is located at the 7-position and is selected from methoxy, ethoxy, propoxy, butoxy, pentoxy, pyrrolidin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy, 3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy

and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH and N(CH₃),

and wherein any terminal CH₃ group within a (1-6C)alkoxy chain in a R¹ substituent optionally bears on the terminal CH₃ group a substituent selected from hydroxy, amino and N-(1-methylpyrrolidin-3-yl)-N-methylamino,

and wherein any pyrrolidinyl or piperidinyl group within a R¹ substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,

and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl, 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl;

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the Q¹-Z- group is selected from cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxodotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy, 5 pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy and azetidin-3-yloxy,

and wherein the azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within the Q¹-Z- group is optionally N- substituted by a substituent selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, allyl, 2-propynyl, acetyl, propionyl, 10 methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-di-methylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-di-methylcarbamoyl)ethyl, acetylmethyl, 2-acetylethyl, methoxycarbonylmethyl and 2-methoxycarbonylethyl,

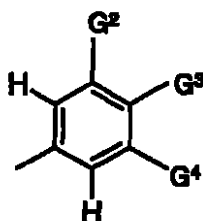
15 and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

R³ is hydrogen;

L is a direct bond or CH(CH₃); and

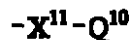
Q² is an aryl group of formula Ib

20



Ib

wherein G³ is selected from hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, methyl, ethyl, and ethynyl, or from a group of the formula:



25 wherein X¹¹ is a direct bond or is selected from O, S, SO₂, N(R²⁰), CO, CH(OR²⁰), C(R²⁰)₂O, C(R²⁰)₂NR²⁰, and C(R²⁰)₂S, wherein R²⁰ is hydrogen, methyl or ethyl, and Q¹⁰ is a phenyl, benzyl or 2-phenylethyl group which is optionally substituted with 1 or 2 substituents selected

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from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl, isopropyl, vinyl, ethynyl and cyano,

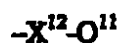
or Q^{10} is a heteroaryl moiety selected from furyl, furylmethyl, 2-(furyl)ethyl, thienyl, thienylmethyl, 2-(thienyl)ethyl, oxazolyl, oxazolylmethyl, 2-(oxazolyl)ethyl, isoxazolyl, isoxazolylmethyl, 2-(isoxazolyl)ethyl, imidazolyl, imidazolylmethyl, 2-(imidazolyl)ethyl, thiazolyl, thiazolylmethyl, 2-(thiazolyl)ethyl, 1,2,4-triazolyl, 1,2,4-triazolylmethyl, 2-(1,2,4-triazolyl)ethyl, 1,2,5-thiadiazolyl, 1,2,5-thiadiazolylmethyl, 2-(1,2,5-thiadiazolyl)ethyl, pyridyl, pyridylmethyl, 2-(pyridyl)ethyl, pyrimidinyl, pyrimidinylmethyl, 2-(pyrimidinyl)ethyl, 1,3-benzodioxolyl, 1,3-benzodioxolylmethyl, 2-(1,3-benzodioxolyl)ethyl, quinoliny, quinolinylmethyl, 2-(quinoliny)ethyl, isoquinoliny, isoquinolinylmethyl, 2-(isoquinoliny)ethyl, quinazoliny, quinazolinylmethyl and 2-(quinazoliny)ethyl, which is optionally substituted with one or two substituents selected from fluoro, chloro, bromo, nitro, methyl, trifluoromethyl, ethyl, isopropyl, methoxy and ethoxy;

or when X^{11} is CO, Q^{10} may also be a 5 to 10 membered nitrogen containing heterocyclic group linked to X^{11} by a nitrogen atom, said nitrogen containing heterocyclic group optionally bearing 1 or 2 substituents selected from fluoro, chloro, cyano, methyl, amino, methylamino and di-methylamino,

and each of G^2 and G^4 independently is selected from hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, methyl and ethynyl,

or G^3 and G^4 together form a group of formula:- $-NH-CH=CH-$, $-CH=CH-NH-$, $-NH-N=CH-$, $-CH=N-NH-$, $-S-N=CH-$ or $-CH=N-S-$,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 are linked together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group of the formula:



wherein X^{12} is a direct bond or is selected from SO_2 and CO, wherein Q^{11} is phenyl, benzyl, 2-phenylethyl, 2-furyl, furfuryl, 3-furyl, 3-furylmethyl, 2-oxazolyl, 4-oxazolyl, 2-oxazolylmethyl, 4-oxazolylmethyl, 2-imidazolyl, 4-imidazolyl, 2-imidazolylmethyl, 4-imidazolylmethyl, 2-, 3- or 4-pyridyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 2-, 4- or 5-pyrimidinyl, 2-, 4- or 5-pyrimidinylmethyl, 2-(2-, 4- or 5-pyrimidinyl)ethyl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-ylmethyl, triazol-3-ylmethyl, 1,2,4-triazol-5-yl, 2-thienyl, 3-thienyl, 2-thienylmethyl, 3-thienylmethyl, 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl,

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2-thiazolyl, 4-thiazolyl, 2-thiazolylmethyl, 4-thiazolylmethyl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-3-ylmethyl, 2-(1,2,5-thiadiazol-3-yl)ethyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, hydroxy, methyl and ethyl,

- 5 and the 9-membered bicyclic heteroaryl ring formed when G³ and G⁴ together are linked optionally bears on an available carbon atom in the heteroaryl portion of the bicyclic ring 1 substituent selected from fluoro, chloro, bromo, cyano, hydroxy, amino, methyl, ethyl, isopropyl, vinyl, ethynyl, methylamino and di-methylamino; provided that when L is a direct bond, at least one of G², G³ and G⁴ is other than H;
- 10 or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

- m is 0 or 1 and the R¹ group, when present, is located at the 7-position and is selected from methoxy, 2-methoxyethoxy, 3-(R)-dimethylaminopyrrolidin-1-yl,
- 15 1-methylpiperidin-4-ylmethoxy, 3-(N-(2-hydroxyethyl)-N-methylamino)propoxy, 2-(N-(2-methoxyethyl)-N-methylamino)ethoxy, 2-(N-(2-hydroxyethyl)-N-methylamino)ethoxy, 3-(N-(2-dimethylaminoethyl)-N-methylamino)propoxy, 2-(N-(2-dimethylaminoethyl)-N-methylamino)ethoxy, 3-pyrrolidin-1-ylpropoxy, 3-(3-hydroxypyrrolidin-1-yl)propoxy, 2-pyrrolidin-1-ylethoxy, 2-(3-hydroxypyrrolidin-1-yl)ethoxy, 2-(3-dimethylaminopyrrolidin-1-
- 20 yl)ethoxy, 3-(3-dimethylaminopyrrolidin-1-yl)propoxy, 3-(N-methyl-N-(1-methylpyrrolidin-3-yl)amino)propoxy, 2-(N-methyl-N-(1-methylpyrrolidin-3-yl)amino)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-homopiperidinoethoxy, 3-homopiperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy,
- 25 3-(4-isopropylpiperazin-1-yl)propoxy, 2-(4-isopropylpiperazin-1-yl)ethoxy, 3-(4-(2-methoxyethyl)piperazin-1-yl)propoxy, 2-(4-(2-methoxyethyl)piperazin-1-yl)ethoxy, 2-(4-(2-morpholinoethyl)piperazin-1-yl)ethoxy, 3-(4-(2-morpholinoethyl)piperazin-1-yl)propoxy, 2-(4-tetrahydrofurfuryl)piperazin-1-ylethoxy,
- 30 3-(4-tetrahydrofurfuryl)piperazin-1-ylpropoxy, 2-(4-(1-methylpiperidin-4-yl)piperazin-1-ylethoxy, 3-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)propoxy, 2-(4-methylhomopiperazin-1-yl)ethoxy, 3-(4-methylhomopiperazin-1-yl)propoxy,

the Q¹-Z- group is selected from cyclopentyloxy,

1-methylazetidin-3-yloxy, 1-isopropylazetidin-3-yloxy, tetrahydrothien-3-yloxy,

1-oxotetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, tetrahydrofuran-3-yloxy,

1-methylpyrrolidin-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy,

5 1-oxotetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, piperidin-4-yloxy,

1-methylpiperidin-4-yloxy, 1-ethylpiperidin-4-yloxy, 1-propylpiperidin-4-yloxy,

1-(2-methoxyethyl)piperidin-4-yloxy, 1-acetyl piperidin-4-yloxy,

1-acetylmethylpiperidin-4-yloxy, 1-allylpiperidin-4-yloxy, 1-(2-propynyl)piperidin-4-yloxy,

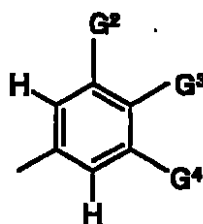
1-methoxycarbonylmethylpiperidin-4-yloxy, 1-carbamoylmethylpiperidin-4-yloxy and

10 1-methanesulphonylpiperidin-4-yloxy;

R³ is hydrogen;

L is a direct bond or CH(CH₃); and

Q² is an aryl group of formula Ib



Ib

15

wherein G³ is selected from hydrogen, fluoro, chloro, bromo, methyl, and ethynyl, or from a group of the formula:



wherein X¹¹ is a direct bond or is selected from O, S, N(R²⁰), C(R²⁰)₂, N(R²⁰) and CO, wherein

20 R²⁰ is hydrogen or methyl, and Q¹⁰ is selected from phenyl or benzyl, 2-thienyl, 2-thienylmethyl, 2-1H-imidazolyl, 2-1H-imidazolylmethyl, 3-isoxazolylmethyl, 4-thiazolyl, 3-(1,2,5-thiadiazolyl), 2-pyridyl, 2-pyridylmethyl, 3-pyridyl, 3-pyridylmethyl, 4-pyridyl, 4-pyridylmethyl and 8-quinoliny, which is optionally substituted by 1 or 2 substituents selected from fluoro, chloro, methyl, isopropyl, trifluoromethyl, nitro and cyano,

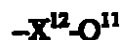
25 or when X¹¹ is CO, Q¹⁰ may also be selected from pyrrolidin-1-yl, piperidino, homopiperidino, morpholino, piperazin-1-yl, homopiperazin-1-yl, decahydroquinolin-1-yl and decahydroquinolin-1-yl,

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and each of G^2 and G^4 independently is selected from hydrogen, fluoro, chloro, bromo, trifluoromethyl, methyl and ethynyl,

or G^3 and G^4 together form a group of formula: -NH-CH=CH-, -NH-N=CH- or -S-N=CH-,

- 5 and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 are linked together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group of the formula:



- wherein X^{12} is a direct bond or is SO_2 , and Q^{11} is phenyl, benzyl, or 2-pyridylmethyl which
10 optionally bears a fluoro substituent,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 together are linked optionally bears at the 3-position a chloro substituent;

provided that when L is a direct bond, at least one of G^2 , G^3 and G^4 is other than H; or a pharmaceutically acceptable salt thereof.

- 15 A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 0 or 1 and the R^1 group, when present, is located at the 7-position and is selected from methoxy, 2-methoxyethoxy and 3-(R)-dimethylaminopyrrolidin-1-yl;

the Q^1 -Z- group is selected from piperidin-4-yloxy, 1-methylpiperidin-4-yloxy and

- 20 tetrahydropyran-4-yloxy;

the Q^2 LNR³ group is selected from 3-chloroanilino, 3-bromoanilino, 3-cyanoanilino, 3-methylanilino, 3-chloro-4-fluoroanilino, indol-5-ylamino, 3-chloroindol-5-ylamino, 1-(3-fluorobenzyl)indazol-5-ylamino, 3-chloro-4-phenoxyanilino, 3-chloro-4-(3-fluorobenzoyloxy)anilino, 3-chloro-4-((decahydroquinolin-1-yl)carbonyl)anilino, 3-chloro-4-

- 25 ((decahydroisoquinolin-2-yl)carbonyl)anilino, 3-chloro-4-((3-methylpiperidin-1-yl)carbonyl)anilino and 3-ethynyl-4-((decahydroquinolin-1-yl)carbonyl)anilino;

or a pharmaceutically acceptable acid-addition salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

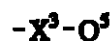
- 30 m is 0 or 1 and the R^1 group, when present, is located at the 7-position and is selected from (1-6C)alkoxy, (2-6C)alkenyloxy and (2-6C)alkynyloxy, or from a group of the formula :



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wherein X^1 is a direct bond or is O, and Q^3 is heterocyclyl or heterocyclyl-(1-6C)alkyl,
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent
are optionally separated by the insertion into the chain of a group selected from O, and $N(R^5)$,
wherein R^5 is hydrogen or (1-6C)alkyl,

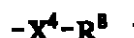
- 5 and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each
said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent
selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or
from a group of the formula :



- 10 wherein X^3 is a direct bond or is $N(R^7)$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^3 is
heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or
3 substituents, which may be the same or different, selected from halogeno, hydroxy, amino,
(1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

- 15 (1-6C)alkoxycarbonyl, or from a group of the formula:



wherein X^4 is a direct bond and R^8 is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
carbamoyl-(1-6C)alkyl, N -(1-6C)alkylcarbamoyl-(1-6C)alkyl,

N,N -di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, or from a group of the formula :

- 20 $-X^5-Q^6$

wherein X^5 is a direct bond and Q^6 is heterocyclyl or heterocyclyl-(1-6C)alkyl which
optionally bears 1 or 2 substituents, which may be the same or different, selected from
hydroxy, amino, (1-6C)alkyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 oxo

- 25 substituent;

Z is O;

Q^1 is selected from azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl,
tetrahydrofuran-3-yl, tetrahydropyran-3-yl and tetrahydropyran-4-yl (conveniently
tetrahydrofuran-3-yl, tetrahydropyran-4-yl or more conveniently piperidin-4-yl), and

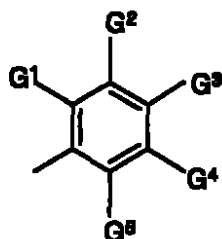
- 30 wherein any NH group within a heterocyclyl group in Q^1 optionally bears a substituent
selected from methyl, ethyl, allyl, 2-methoxyethyl, carbamoylmethyl, N -
methylcarbamoylmethyl, N,N -dimethylcarbamoylmethyl and methoxycarbonylmethyl,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 oxo substituent;

R² and R³ are hydrogen;

L is a direct bond;

5 Q² is an aryl group of formula Ia



Ia

wherein G¹, G² and G⁵ are hydrogen,

G⁴ is selected from hydrogen, halogeno, (1-6C)alkyl, (2-8C)alkenyl and (2-8C)alkynyl and

10 G³ is selected from hydrogen, halogeno and hydroxy,

with the proviso that G³ and G⁴ are not both hydrogen,

or G³ and G⁴ together form a group of formula :- -NH-CH=CH- or -NH-N=CH-

and the 9- membered bicyclic heteroaryl ring formed when G³ and G⁴ together are linked optionally bears on the heteroaryl portion of the bicyclic ring 1 or 2 substituents, which
15 may be the same or different, selected from halogeno, cyano and (1-6C)alkyl;
or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 0 or 1 and the R¹ group, when present is located at the 7 position and is selected
20 from (1-3C)alkoxy, (1-3C)alkoxy(1-3C)alkoxy and a group of the formula :



wherein X¹ is O and Q³ is 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-4-ylmethyl, 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-piperazin-1-ylethyl,
25 3-piperazin-1-ylpropyl, 2-homopiperazin-1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein any heterocyclyl group within a R¹ substituent optionally bears a substituent selected from hydroxy, carbamoyl, methyl, ethyl, allyl, 2-propynyl, acetyl,

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N-methylcarbamoyl N,N-dimethylcarbamoyl, 2-methoxyethyl, carbamoylmethyl, N,N-dimethylcarbamoylmethyl, acetylmethyl and cyanomethyl,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 oxo substituent, or

5 R¹ is 3-(R)-dimethylaminopyrrolidin-1-yl;

Z is O;

Q¹ is selected from azetidin-3-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl and tetrahydropyran-4-yl (conveniently piperidin-4-yl or tetrahydrofuran-3-yl), and

10 wherein any NH group within a heterocyclyl group in Q¹ optionally bears a substituent selected from methyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl and methoxycarbonylmethyl,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 oxo substituent;

15 R² is hydrogen; and

Q²LN(R³) is selected from 3-chloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-chloroanilino, 3-methylanilino and 3-ethynylanilino;

or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I

20 wherein:

m is 1 and the R¹ group is located at the 7 position and is selected from methoxy, 2-methoxyethoxy and a group of the formula :



wherein X¹ is O and Q³ is 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy,

25 3-piperidinopropoxy, and 3-piperazin-1-ylpropoxy,

and wherein any heterocyclyl group within a R¹ substituent optionally bears a substituent selected from hydroxy, carbamoyl, methyl, ethyl, allyl, acetyl, N-methylcarbamoyl N,N-dimethylcarbamoyl, 2-methoxyethyl, carbamoylmethyl and N,N-dimethylcarbamoylmethyl,

30 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 oxo substituent;

Z is O;

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Q^1 is selected from piperidin-3-yl, piperidin-4-yl, tetrahydrofuran-3-yl, tetrahydropyran-3-yl and tetrahydropyran-4-yl (conveniently piperidin-4-yl or tetrahydrofuran-3-yl), and

wherein any NH group within a heterocyclyl group in Q^1 optionally bears a substituent
5 selected from methyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl and methoxycarbonylmethyl,
and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1 oxo substituent;

R^2 is hydrogen; and

10 $Q^2LN(R^3)$ is selected from 3-chloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-chloroanilino, 3-methylanilino and 3-ethynylanilino;
or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

15 R^4 is hydrogen;

$Q^2LN(R^3)$ is selected from 3-chloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-chloroanilino, 3-methylanilino and 3-ethynylanilino (conveniently 3-chloro-4-fluoroanilino or 3-ethynylanilino); and

20 (I) m is 1 and the R^1 group is located at the 7 position and is selected from methoxy and 2-methoxyethoxy;

Z is O;

Q^1 is selected from Q^1 is selected from piperidin-4-yl and piperidin-3-yl (conveniently piperidin-4-yl), and

25 wherein any NH group within a piperidinyl group in Q^1 optionally bears a substituent selected from methyl, carbamoylmethyl and N,N-dimethylcarbamoylmethyl, or

(II) m is 1 and the R^1 group is located at the 7 position and is selected from 3-pyrrolidin-1-ylpropoxy, 3-morpholinopropoxy and 3-piperazin-1-ylpropoxy,

30 and wherein any NH group within a piperazinyl in R^1 optionally bears a substituent selected from methyl, carbamoylmethyl and N,N-dimethylcarbamoylmethyl,

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and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 oxo substituent;

Z is O; and

Q¹ is selected from tetrahydropyran-3-yl, tetrahydropyran-4-yl and tetrahydrofuran-3-yl
5 (conveniently tetrahydrofuran-3-yl),

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 oxo substituent;

or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I

10 wherein:

m is 1 and the R¹ group is located at the 7 position and is selected from
3-pyrrolidin-1-ylpropoxy, 3-pyrrolidin-2-ylpropoxy, 3-pyrrolidin-3-ylpropoxy,
3-morpholinopropoxy, 3-piperidinopropoxy, 3-piperidin-2-ylpropoxy,
3-piperidin-3-ylpropoxy, 3-piperidin-4-ylpropoxy and 3-piperazin-1-ylpropoxy,

15 and wherein any heterocyclyl group within a R¹ substituent optionally bears a substituent selected from hydroxy, carbamoyl, methyl, ethyl, allyl, acetyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, 2-methoxyethyl, carbamoylmethyl, N,N-dimethylcarbamoylmethyl, acetylmethyl and cyanomethyl,

and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 oxo

20 substituent;

Z is O;

Q¹ is tetrahydrofuran-3-yl, tetrahydropyran-4-yl or tetrahydropyran-3-yl,

R² is hydrogen; and

Q²LN(R³) is selected from 3-chloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-
25 chloroanilino, 3-methylanilino and 3-ethynylanilino;

or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I

wherein:

m is 0 or 1 and the R¹ group, when present is located at the 7 position and is selected from (1-
30 3C)alkoxy and (1-3C)alkoxy(1-3C)alkoxy (for example methoxy or 2-methoxyethoxy);

Z is O;

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Q^1 is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl (conveniently piperidin-4-yl), and

wherein any NH group within a pyrrolidinyl or piperidinyl group in Q^1 optionally bears a substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl,

5 ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, or from a group of the formula:



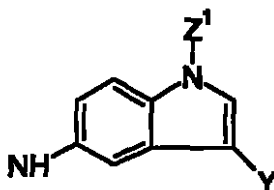
wherein X^8 is a direct bond, and R^{15} is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methylcarbamoyl-(1-3C)alkyl,

10 N,N-dimethylcarbamoyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or methoxycarbonyl-(1-3C)alkyl, and wherein any pyrrolidinyl or piperidinyl group within the Q^1 -Z- group optionally bears 1 oxo substituent;

R^2 is hydrogen; and

$Q^2LN(R^3)$ is a group of the formula Ic:

15



Ic

wherein Z^1 is hydrogen or (1-4C)alkyl (conveniently hydrogen), and

Y is selected from hydrogen, halogeno, (1-4C)alkyl and cyano (conveniently hydrogen, 20 chloro or bromo, more conveniently chloro or bromo); or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 0 or 1 and the R^1 group, when present is located at the 7 position and is methoxy;

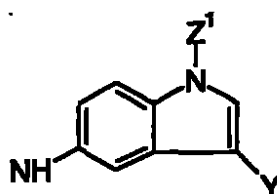
25 Z is O;

Q^1 is 1-methylpiperidin-4-yl;

R^2 is hydrogen; and

$Q^2LN(R^3)$ is a group of the formula Ic:

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Ic

wherein Z^1 is hydrogen, and

Y is selected from hydrogen, chloro and bromo;

5 or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 1 and the R^1 group is located at the 7 position and is selected from (1-3C)alkoxy and (1-3C)alkoxy(1-3C)alkoxy (for example methoxy or 2-methoxyethoxy);

10 Z is O;

Q^1 is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl (conveniently piperidin-4-yl), and

wherein any NH group within a pyrrolidinyl or piperidinyl group in Q^1 optionally bears a substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl,

15 ethoxycarbonyl, N-methoxycarbonyl and N,N-dimethoxycarbonyl, or from a group of the formula:



wherein X^8 is a direct bond, and R^{15} is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methoxycarbonyl-(1-3C)alkyl,

20 N,N-dimethoxycarbonyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or methoxycarbonyl-(1-3C)alkyl,

and wherein any pyrrolidinyl or piperidinyl group within the Q^1 -Z- group optionally bears 1 oxo substituent;

R^2 and R^3 are hydrogen;

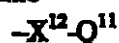
L is a direct bond; and

25 Q^2 is a group of formula Ia as hereinbefore defined wherein:

G^1 , G^2 and G^5 are hydrogen, and

G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$, and the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is substituted at the 1-position by a group of the formula:

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wherein X^{12} is a direct bond and Q^{11} is benzyl which is optionally substituted by 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, methyl and ethyl, (for example Q^{11} is 2-fluorobenzyl or 3-fluorobenzyl), and

- 5 and wherein the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is optionally substituted at the 3-position by a substituent selected from chloro and bromo;
or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I

- 10 wherein:

m is 1 and the R^1 group is located at the 7 position and is methoxy;

Z is O;

Q^1 is 1-methylpiperidin-4-yl;

R^2 and R^3 are hydrogen;

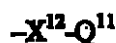
- 15 L is a direct bond; and

Q^2 is a group of formula Ia as hereinbefore defined wherein:

G^1 , G^2 and G^5 are hydrogen, and

G^3 and G^4 together form a group of the formula: $-NH-CH=CH-$, and the indolyl ring so formed by G^3 and G^4 together with the carbon atoms to which they are attached is substituted

- 20 at the 1-position by a group of the formula:



wherein X^{12} is a direct bond and Q^{11} is benzyl which is optionally substituted by 1 fluoro substituent, (for example Q^{11} is 2-fluorobenzyl or 3-fluorobenzyl);

or a pharmaceutically acceptable salt thereof.

- 25 A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 1 and the R^1 group is located at the 7 position and is selected from (1-3C)alkoxy, (1-3C)alkoxy(1-3C)alkoxy and piperidin-4-ylmethoxy (for example R^1 is methoxy or 2-methoxyethoxy);

- 30 Z is O;

Q^1 is selected from pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl and tetrahydropyran-4-yl (conveniently piperidin-4-yl), and

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wherein any NH group within a pyrrolidinyl or piperidinyl group in Q¹ optionally bears a substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, or from a group of the formula:



wherein X⁸ is a direct bond, and R¹⁵ is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methylcarbamoyl-(1-3C)alkyl, N,N-di-methylcarbamoyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or methoxycarbonyl-(1-3C)alkyl, and wherein any pyrrolidinyl or piperidinyl group within the Q¹-Z- group optionally bears 1

10 oxo substituent;

R² and R³ are hydrogen;

L is a direct bond; and

Q² is a group of formula Ia wherein:

G¹, G² and G⁵ are hydrogen,

15 G⁴ is selected from chloro, methyl and ethynyl, and

G³ is a group of the formula:



wherein X¹¹ is O and Q¹⁰ is benzyl which is optionally substituted by 1 or 2 substituents, which may be the same or different, selected from fluoro, cyano and methyl;

20 or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 1 and the R¹ group is located at the 7 position and is methoxy;

Z is O;

25 Q¹ is 1-methylpiperidin-4-yl;

R² and R³ are hydrogen;

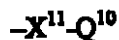
L is a direct bond; and

Q² is a group of formula Ia wherein:

G¹, G² and G⁵ are hydrogen,

30 G⁴ is chloro, and

G³ is a group of the formula:



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wherein X^{11} is O and Q^{10} is benzyl which is optionally substituted by 1 fluoro substituent (for example $-X^{11}-Q^{10}$ is 3-fluorobenzyl or benzyl);

or a pharmaceutically acceptable salt thereof.

A further embodiment of the invention is a quinazoline derivative of the Formula I

5 wherein:

m is 1 and the R^1 group is located at the 7 position and is selected from (1-3C)alkoxy and (1-3C)alkoxy(1-3C)alkoxy (for example methoxy or 2-methoxyethoxy);

Z is O;

10 Q^1 is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl (conveniently piperidin-4-yl), and

wherein any NH group within a pyrrolidinyl or piperidinyl group in Q^1 optionally bears a substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, or from a group of the formula:

15 $-X^8-R^{15}$

wherein X^8 is a direct bond, and R^{15} is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methylcarbamoyl-(1-3C)alkyl,

N,N-di-methylcarbamoyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or methoxycarbonyl-(1-3C)alkyl,

20 and wherein any pyrrolidinyl or piperidinyl group within the Q^1 -Z- group optionally bears 1 oxo substituent;

R^2 and R^3 are hydrogen;

L is a direct bond; and

Q^2 is a group of formula Ia wherein:

G^1 , G^2 and G^5 are hydrogen,

25 G^4 is selected from chloro and methyl, and

G^3 is a group of the formula:

$-X^{11}-Q^{10}$

wherein X^{11} is O and Q^{10} is selected from isoxazolylmethyl and thiazolylmethyl (for example 3-isoxazolylmethyl or 4-thiazolylmethyl), and wherein the heteroaryl group within Q^{10}

30 optionally bears a methyl substituent;

or a pharmaceutically acceptable salt thereof.

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A further embodiment of the invention is a quinazoline derivative of the Formula I wherein:

m is 1 and the R¹ group is located at the 7 position and is methoxy;

Z is O;

5 Q¹ is 1-methylpiperidin-4-yl;

R² and R³ are hydrogen;

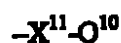
L is a direct bond; and

Q² is a group of formula Ia wherein:

G¹, G² and G³ are hydrogen,

10 G⁴ is selected from chloro and methyl (conveniently methyl), and

G⁵ is a group of the formula:



wherein X¹¹ is O and Q¹⁰ is selected from 3-isoxazolylmethyl and 4-thiazolylmethyl, and

wherein heteroaryl group within Q¹⁰ optionally bears 1 methyl substituent (for example Q¹⁰ is

15 5-methyl-isoxazol-3-ylmethyl, or 4-thiazolylmethyl);

or a pharmaceutically acceptable salt thereof.

A further particular preferred compound of the invention is, for example, a quinazoline derivative of the Formula I selected from:

4-(3-Chloroanilino)-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-

20 4-yloxy)quinazoline;

4-(3-Chloroindol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(3-Bromoanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(3-Chloroindol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(3-Ethynylanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

25 4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(3-Chloroanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

7-Methoxy-4-(3-methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(Indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(3-Bromoanilino)-7-(2-methoxyethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline;

30 4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline;

4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-(piperidin-1-

yl)propoxy)quinazoline;

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XZ

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4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(2-(4-isopropyl-piperazin-1-yl)ethoxy)quinazoline;

4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-hydroxyethyl)-N-methylamino)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline;

5 4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-dimethylaminoethyl)-N-methylamino)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline; and

4-(3-Chloro-4-fluoroanilino)-7-(3-(4-methylpiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline;

or a pharmaceutically acceptable acid addition salt thereof;

10 A further particular preferred compound of the invention is, for example, a quinazoline derivative of the Formula I selected from:

4-(3-Bromoanilino)-7-(3-(*R*)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(3-Bromoindol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

15 4-(3-Chloro-4-benzyloxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(3-Methyl-4-(5-methylisoxazol-3-ylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

20 4-(3-Methyl-4-(thiazol-4-ylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

4-(1-(3-Fluorobenzyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

and

4-(1-(2-Fluorobenzyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

25 or a pharmaceutically acceptable acid addition salt thereof.

A further particular preferred compound of the invention is, for example, a quinazoline derivative of the Formula I selected from :

4-(3-Chloro-4-fluoroanilino)-7-(3-morpholinopropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline;

30 4-(3-Chloro-4-fluoroanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline;

2-[4-(4-(3-Chloro-4-fluoroanilino)-7-methoxyquinazolin-5-yloxy)piperidin-1-yl]acetamide;

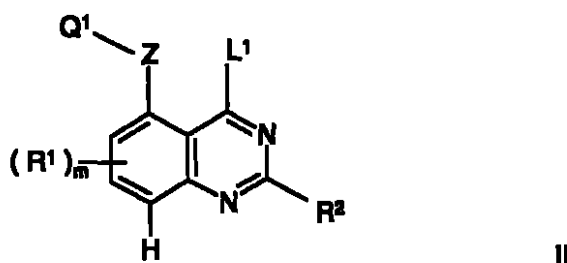
4-(3-Chloro-4-fluoroanilino)-7-(2-methoxyethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline;
and

4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(N,N-dimethylcarbamoylmethyl)piperazin-1-yl)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline;

5 or a pharmaceutically acceptable acid addition salt thereof.

A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated
10 by the following representative process variants in which, unless otherwise stated, Q^1 , Z, m, R^1 , R^2 , R^3 , L and Q^2 have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials
15 are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Process (a) The reaction, conveniently in the presence of a suitable base, of a quinazoline of the Formula II



20 wherein L^1 is a displaceable group and Q^1 , Z, m, R^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula



wherein Q^2 , L and R^3 have any of the meanings defined hereinbefore except that any
25 functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline

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earth metal carbonate, for example sodium carbonate, potassium carbonate, calcium carbonate, or, for example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group L^1 is, for example, a halogeno, alkoxy, aryloxy, mercapto, alkylthio, arylthio, alkylsulphinyl, arylsulphinyl, alkylsulphonyl, arylsulphonyl or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methylthio, methanesulphonyl, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, preferably in the range 40 to 80°C.

The quinazoline of the Formula II may also be reacted with a compound of the formula Q^2LNHR^3 in the presence of a protic solvent such as isopropanol, conveniently in the presence of an acid, for example hydrogen chloride gas in diethyl ether or dioxane, or hydrochloric acid. Alternatively, this reaction may be conveniently carried out in an aprotic solvent, such as dioxane or a dipolar aprotic solvent such as N,N-dimethylacetamide in the presence of an acid, for example hydrogen chloride gas in diethyl ether or dioxane, or hydrochloric acid. The above reactions are conveniently carried out at a temperature in the range, for example, 0 to 150°C, preferably at or near the reflux temperature of the reaction solvent.

The quinazoline derivative of the Formula II, wherein L^1 is halogeno, may be reacted with a compound of the formula Q^2LNHR^3 in the absence of an acid or a base. In this reaction displacement of the halogeno leaving group L^1 results in the formation of the acid HL^1 in-situ and the auto-catalysis of the reaction. Conveniently the reaction is carried out in a suitable inert organic solvent, for example iso propanol, dioxane or N,N-dimethylacetamide. Suitable conditions for this reaction are as described above

The quinazoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula $H-L^1$ wherein L^1 has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

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Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with *minimum* disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl,

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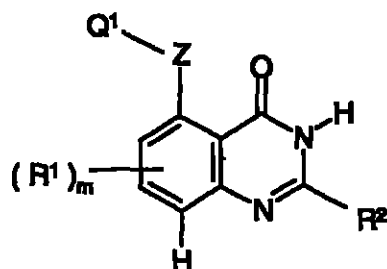
2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and
 5 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); lower alkanoyloxyalkyl groups (for example pivaloyloxymethyl); trialkylsilyl (for example
 10 trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylenedene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for
 15 groups such as 2-nitrobenzyloxycarbonyl. For example a tert butoxycarbonyl protecting group may be removed from an amino group by an acid catalysed hydrolysis using trifluoroacetic acid.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and
 20 reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

Quinazoline starting materials of the Formula II may be obtained by conventional procedures. For example, a 3,4-dihydroquinazolin-4-one of Formula III



III

25 wherein *m*, *R*¹, *Q*¹, *Z* and *R*² have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional

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means. The reaction is conveniently carried out in a suitable inert solvent, for example 1,2-dichloroethane or *N,N*-dimethylformamide conveniently in the presence of an base such as an organic base, for example di-isopropylethylamine. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 150°C, preferably at or near the reflux

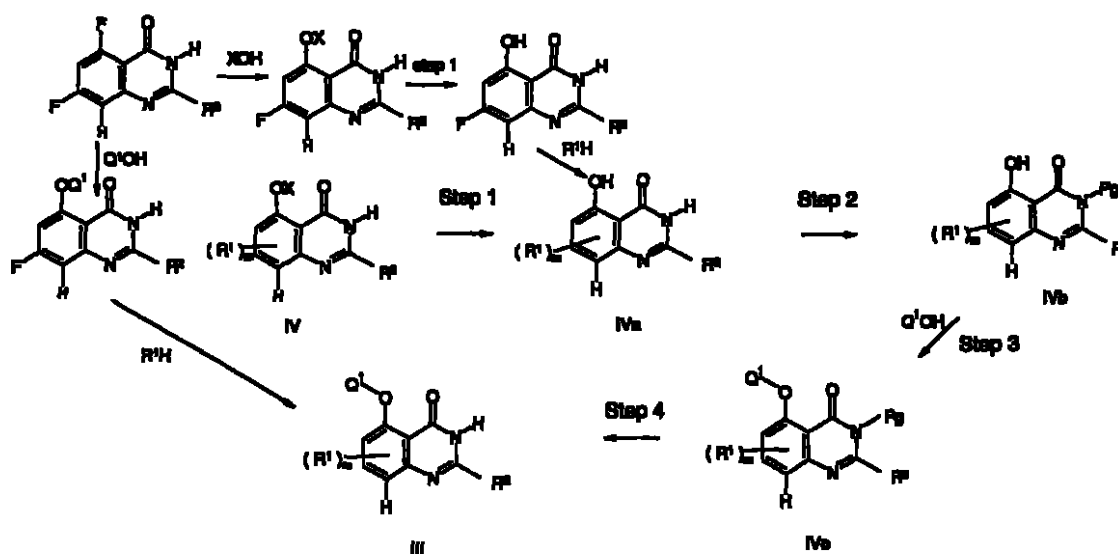
5 temperature of the reaction solvent.

The 4-chloroquinazoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinazoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as *N,N*-dimethylformamide.

10 The compound of Formula I may be also be prepared using a telescoped process starting from the compound of Formula III, wherein the compound of the Formula Q^2LNHR^3 is reacted with the compound of Formula II following halogenation of the compound of Formula III. The use of such a telescoped process avoids the need to isolate the compound of Formula II prior to reaction with the compound of formula Q^2LNHR^3 .

15 The 3,4-dihydroquinazolin-4-one of Formula III may be obtained using conventional procedures. For example when Z is an oxygen atom the compound of Formula III may be prepared as illustrated by Reaction Scheme 1 starting with the compound of Formula IV.

Reaction Scheme 1



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wherein R^1 , R^2 and Q^1 are as hereinbefore defined, X is a suitable hydroxy protecting group such as (1-6C)alkyl (for example methyl) or benzyl, and Pg is a suitable amine protecting group.

Notes:

5 Step (1)

When X is (1-6C)alkyl, it may be may be cleaved from the compound of formula IV by conventional methods, such as by treatment of the compound of Formula IV with, for example:

- (i) an alkali metal (1-6C)alkylsulphide such as sodium ethanethiolate;
- 10 (ii) an alkali metal diarylphosphide such as lithium diphenylphosphide;
- (iii) a boron or aluminium trihalide such as boron tribromide;
- (iv) magnesium bromide, preferably in the presence of a suitable base, such as an organic base, for example pyridine; or
- (v) pyridine hydrochloride in pyridine.

- 15 Generally the cleavage reaction is carried out at a temperature in the range of from, for example, 40 to 150°C.

When X is benzyl, it may be may be cleaved from the compound of formula IV by, for example, acid catalysed hydrolysis, for example by treatment of the compound of Formula IV with trifluoroacetic acid. Conveniently the reaction is carried out at a temperature in the range

20 of 30 to 120°C, for example 70°C.

Step (2)

The protecting group Pg is added to the 3,4-dihydro-5-hydroxyquinazolin-4-one of Formula IVa using conventional techniques. For example a suitable Pg is a pivaloyloxymethyl group that may be added to the compound of Formula IVa by reacting the

25 compound of Formula IVa with chloromethylpivalate in the presence of a suitable base such as sodium hydride.

Step (3)

The Q^1O group may be introduced by coupling the compound of Formula IVb with an alcohol of the Formula Q^1OH in the presence of a suitable dehydrating agent. Suitable

30 conditions for the coupling reaction are described below with reference to process (b).

Step (4)

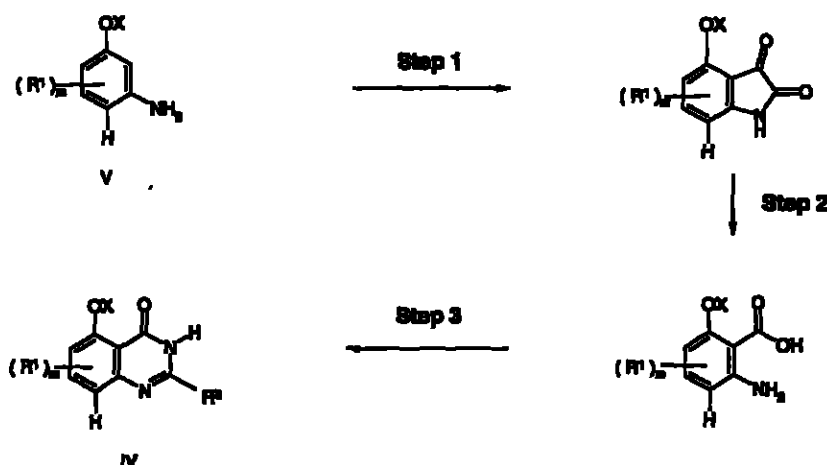
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The protecting group Pg may be removed using conventional methods, for example when Pg is a pivaloyloxymethyl group it may be removed by treating the compound of Formula IVc with a methanolic ammonia solution.

The compound of formula IV may be prepared starting from an aniline of the Formula V as illustrated in Reaction Scheme 2.

Reaction Scheme 2



wherein R^1 , R^2 , m and X are as hereinbefore defined.

10 Notes:

Steps 1 and 2 may be carried out using analogous conditions to the processes described in Organic Syntheses, Coll Vol 1, p 327-330; J Org Chem 1969, 34, 3484-3489.

Step 3 may be carried out using analogous conditions to the process described in J. Org. Chem. 1952, 17, 141-148; J Med Chem 1994, 37, 2106-2111.

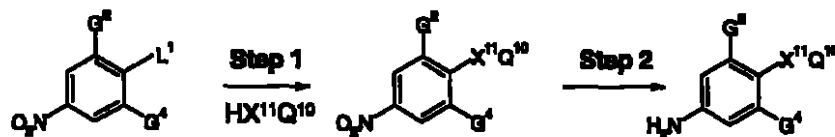
15 Anilines of Formula V are commercially available compounds, or they are known in the literature, or can be prepared using well known processes in the art.

The quinazoline starting materials of the formula II may also be prepared using alternative synthetic routes to those described above using conventional techniques in organic chemistry. Representative examples of suitable synthetic methods for the preparation of the
20 starting quinazoline material of the formula II and the intermediates described above in Reaction Schemes 1 and 2 are provided by the examples herein.

Compounds of the Formula Q^2LNHR^3 are commercially available compounds, or they are known in the literature, or can be prepared using conventional synthetic methods. For example when L is a direct bond and G^3 is a group of the formula $-X^{11}-Q^{10}$ the compound of

the formula Q^2LNHR^3 may be prepared in accordance with Reaction Scheme 3 or Reaction Scheme 4.

Reaction Scheme 3



5 wherein X^{11} is, for example, NR^{20} , O, S or $NR^{20}C(R^{20})_2$ and G^2 , G^4 , L^1 , Q^{10} and R^{20} are as hereinbefore defined, except any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means.

10 Notes

Step 1 may be performed under analogous conditions to those used in process (a) described above. The compounds of the formula $HX^{11}Q^{10}$ are commercially available, or they are known in the literature, or can be prepared using well known processes in the art.

The reduction of the nitro group in step 2 may be carried out under standard
15 conditions, for example by catalytic hydrogenation over a platinum/carbon, palladium/carbon or nickel catalyst, treatment with a metal such as iron, titanium chloride, tin (II) chloride (suitably in the presence of an acid such as HCl), or treatment with another suitable reducing agent such as sodium dithionite.

In an variation of process (a) the reduction of the nitro-compound in step 2 of
20 Reaction Scheme 3 may be carried out as described above, followed directly with reaction with the compound of formula II in a telescoped process, thereby avoiding the need to isolate the compound of the formula Q^2LNHR^3 .

When L is a direct bond and Q^2 is a compound of the formula 1a in which G^3 is a group of the formula $-X^{11}-Q^{10}$ wherein X^{11} is O and Q^{10} is heteroaryl-(1-6C)alkyl or aryl-(1-
25 6C)alkyl the compound of the formula Q^2LNHR^3 may, for example, be prepared by reacting the starting nitro compound shown in Reaction Scheme 3 in which L^1 is OH with a compound of the formula Q^{10} -halide (for example heteroaryl- CH_2 -bromide or benzyl chloride). The nitro group may then be reduced to an amino group by using step 2 of the process in Reaction Scheme 3. Such compounds may also be prepared by reacting the starting nitro compound
30 shown in Reaction Scheme 3 in which L^1 is halide with a compound of the formula $Q^{10}OH$, followed by reduction of the nitro group as described above in Reaction Scheme 3.

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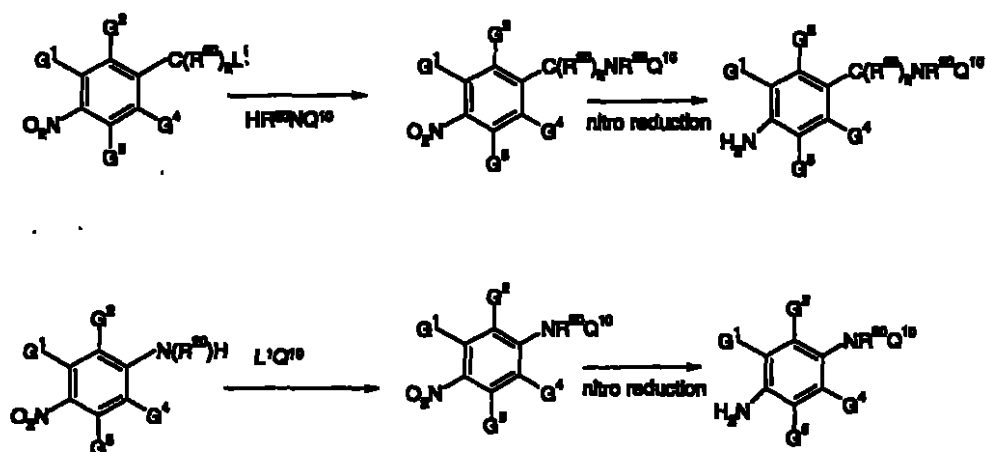
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Compounds of the formula Q^3OH are known or may be prepared using known methods, for example by reduction of the corresponding ester of the formula Q^3COOR , wherein R is, for example (1-6C)alkyl, or benzyl, with a suitable reducing agent, for example sodium borohydride.

- 5 When L is a direct bond and Q^2 is a compound of the formula 1a in which G^3 is a group of the formula $-X^{11}-Q^{10}$ wherein X^{11} is O and Q^{10} is heteroaryl-(1-6C)alkyl or aryl-(1-6C)alkyl the compound of the formula Q^2LNHR^3 may, for example, be prepared by coupling the starting nitro compound shown in Reaction Scheme 3 in which L^1 is OH with a compound of the formula $Q^{10}OH$, conveniently in the presence of a suitable dehydrating agent. Suitable
- 10 conditions for performing this reaction are analogous to those described below in relation to Process(b).

- When L is a direct bond and Q^2 is a compound of the formula 1a in which G^3 is a group of the formula $-X^{11}-Q^{10}$ wherein X^{11} is $C(R^{20})_2NR^{20}$ or NR^{20} and Q^{10} is heteroaryl-(1-6C)alkyl or aryl-(1-6C)alkyl the compound of the formula Q^2LNHR^3 may, for example, be
- 15 prepared according to Reaction Scheme 3a:

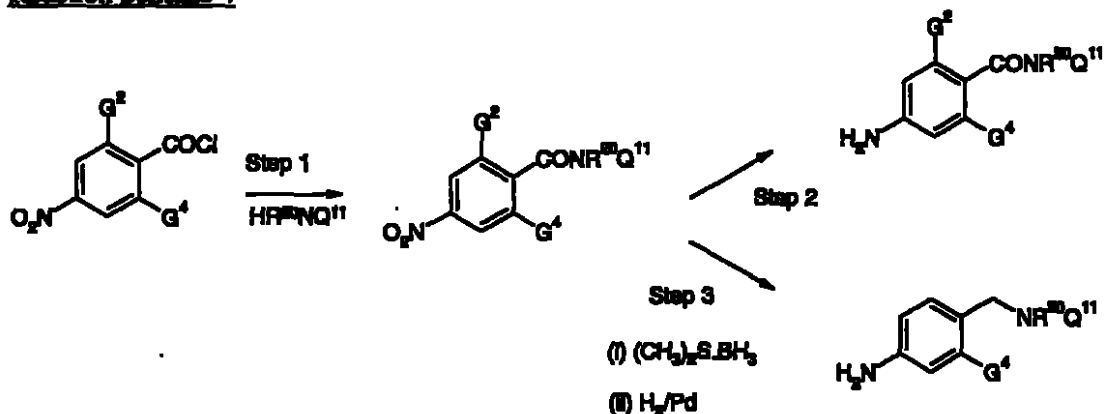
Reaction Scheme 3a



- 20 wherein Q^{10} is heteroaryl-(1-6C)alkyl or aryl-(1-6C)alkyl, and G^1, G^2, G^4, G^5, L^1 and R^{20} are as hereinbefore defined except any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means. The first step of Reaction Scheme 3a may be performed under analogous conditions to those used in process (a) described above. The starting nitro compounds and the compounds of the formula
- 25 $Q^{10}NR^{20}H$ and $Q^{10}L^1$ are commercially available, or they are known in the literature, or can be

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prepared using well known processes in the art. The reduction of the nitro group in step 2 may be carried out under analogous conditions to those described above for Reaction Scheme 3.

Reaction Scheme 4

- 5 wherein G^2 , G^4 , Q^{11} and R^{20} are as hereinbefore defined, except any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means, and L^1 is a suitable leaving group such as halide, for example chloro.

Notes

Suitable for the preparation of those compounds wherein X^{11} is CO or CH_2NR^{20} .

- 10 Step 1 may be carried out under analogous conditions to those used in process (a) described above.

The reduction of the nitro group in step 2 may be carried out as described above in reaction scheme 3.

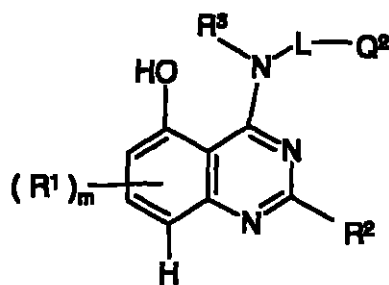
- When L is a direct bond and Q^2 is a compound of the formula Ia in which G^3 is a group of the formula $-X^{11}-Q^{10}$ wherein X^{11} is CO and Q^{10} is a nitrogen containing heterocyclyl group linked to X^{11} by a nitrogen atom, the compound of the formula Q^2NHR^3 may be prepared by coupling the starting nitro compound shown in Reaction Scheme 3 in which L^1 is carboxy with a compound of the formula $Q^{10}H$ in the presence of a suitable coupling agent, for example O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (HATU). Suitable conditions for this reaction are analogous to those described in relation to process (i) below.

Process (b) For the production of those compounds of the Formula I wherein Z is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of an alcohol of the Formula



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wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary with a quinazoline of the Formula VI

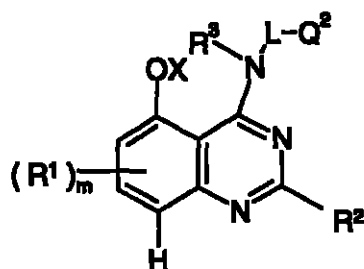


VI

wherein m , R^1 , R^2 , R^3 , L and Q^2 have any of the meanings defined hereinbefore except that
 5 any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of
 10 an azo compound such as diethyl or di-*tert*-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 0 to 150°C, preferably at or near ambient temperature.

The quinazoline of the Formula VI may be obtained by conventional procedures. For
 15 example, by cleavage of the group represented by X from the compound of the Formula VII



VII

wherein X is as defined hereinbefore and m , R^1 , R^2 , R^3 , Q^2 , m and L have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any
 20 protecting group that is present is removed by conventional means.

The cleavage reaction is conveniently carried out as hereinbefore described in relation to step (1) in Reaction Scheme 1.

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The compound of Formula VII may be prepared by for example reacting the compound of the Formula (IV) as hereinbefore defined, with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine. The resulting compound is then reacted with a compound of the Formula

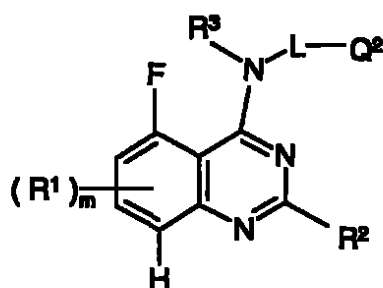


wherein Q^2 , L and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means. The halogenation reaction may be performed under analogous conditions to those described above in relation to the reaction with the compound of the Formula III. The subsequent reaction with the compound of the Formula Q^2LNR^3 may be performed under analogous conditions to those described above in relation to the reaction with the compound of the Formula II.

Process(c) For the production of those compounds of the Formula I wherein Z is O, the reaction, conveniently in the presence of a suitable base, of an alcohol of the Formula



wherein Q^1 has any of the meanings defined hereinbefore except that any functional group is protected if necessary with a quinazoline of the Formula VIII



VIII

wherein m, R^1 , R^2 , R^3 , L and Q^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

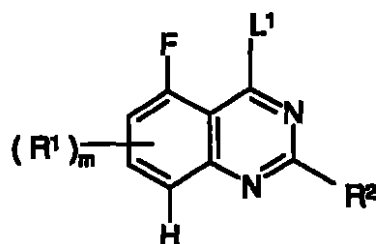
A suitable base includes, for example a strong non-nucleophilic base such as an alkali metal hydride, for example sodium hydride, or an alkali metal amide, for example lithium di-isopropylamide (LDA).

25 The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide,

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N,N-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, preferably in the range 40 to 150°C. This process is particularly suitable for the preparation of those compounds of formula I in which $m=0$.

- 5 The quinazoline of the Formula VIII may be obtained by conventional procedures. For example, a quinazoline of the Formula IX



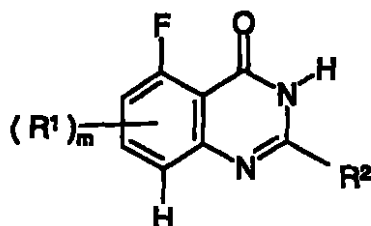
IX

wherein L^1 is a displaceable group as defined hereinbefore (such as halogeno, for example
10 chloro) and m , R^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a compound of the Formula



wherein Q^2 , L and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is
15 removed by conventional means. The reaction may be performed under analogous conditions to those described above under Process (a).

The quinazoline of Formula IX may be obtained using conventional methods, for example a 3,4-dihydroquinazolin-4-one of Formula X



X

- 20 wherein m , R^1 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

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Conveniently compounds of formula VIII may be prepared directly starting from the compound of formula X using a telescoped process. In this process the 3,4-dihydroquinazolin-4-one of Formula X is halogenated as described above using a suitable halogenating agent. The resulting product is then reacted directly with the compound of the formula Q^3LNHR^3 as described above, to give a compound of the formula VIII. This process enables compounds of formula VIII to be prepared without isolating the intermediate compound of the formula IX.

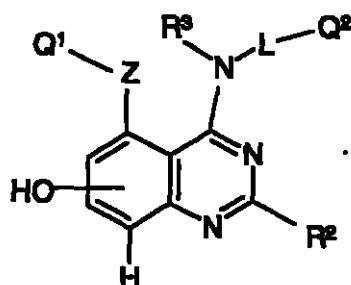
The quinazoline starting materials of Formula X are known or may be prepared using conventional methods. For example the compound of the formula X wherein $m=0$ is described in described in J. Org. Chem. 1952, 17, 164-176.

In an alternative process the 3,4-dihydroquinazolin-4-one of Formula X is reacted with the alcohol of the Formula Q^1-OH as described above to give a compound of Formula III. The compound of Formula III may then be converted to a compound of Formula I by halogenation and reaction with the compound of the formula Q^3LNHR^3 as described above under Process (a).

Process(d) For the production of those compounds of the Formula I wherein m is 1 and R^1 is a group of the formula



wherein Q^3 is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group and X^1 is O, the coupling, conveniently in the presence of a suitable dehydrating agent as defined hereinbefore, of a quinazoline of the Formula XI



XI

wherein Q^1 , Z, L, R^2 , R^3 and Q^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an alcohol of the formula Q^3OH wherein any functional group in Q^3 is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

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The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

- 5 The compound of Formula XI may, for example, be prepared according to process (a) described above.

Process (c) For the production of those compounds of the Formula I wherein R¹ is a hydroxy group, the cleavage of a quinazoline derivative of the Formula I wherein R¹ is a (1-6C)alkoxy or arylmethoxy group.

- 10 The cleavage reaction may conveniently be carried out by any of the many procedures known for such a transformation. The cleavage reaction of a compound of the Formula I wherein R¹ is a (1-6C)alkoxy group may be carried out, for example, by treatment of the quinazoline derivative with an alkali metal (1-6C)alkylsulphide such as sodium ethanethiolate or, for example, by treatment with an alkali metal diarylphosphide such as lithium
- 15 diphenylphosphide. Alternatively the cleavage reaction may conveniently be carried out, for example, by treatment of the quinazoline derivative with a boron or aluminium trihalide such as boron tribromide. The cleavage reaction of a compound of the Formula I wherein R¹ is a arylmethoxy group may be carried out, for example, by hydrogenation of the quinazoline derivative in the presence of a suitable metallic catalyst such as palladium or by reaction with
- 20 an organic or inorganic acid, for example trifluoroacetic acid. Such reactions are preferably carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

- Process (f) For the production of those compounds of the Formula I wherein Q¹, R¹ or Q²
- 25 contains a primary or secondary amino group, the cleavage of the corresponding compound of Formula I wherein Q¹, R¹ or Q² contains a protected primary or secondary amino group.

- Suitable protecting groups for an amino group are, for example, any of the protecting groups disclosed hereinbefore for an amino group. Suitable methods for the cleavage of such amino protecting groups are also disclosed hereinbefore. In particular, a suitable protecting
- 30 group is a lower alkoxycarbonyl group such as a *tert*-butoxycarbonyl group which may be cleaved under conventional reaction conditions such as under acid-catalysed hydrolysis, for example in the presence of trifluoroacetic acid.

Process (g) For the production of those compounds of the Formula I wherein Q¹, R¹ or Q²

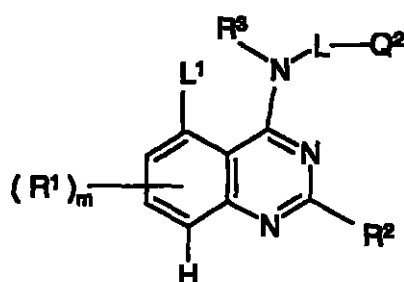
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contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of a quinazoline derivative of the formula I wherein Q¹, R¹ or Q² contains a hydroxy group or a primary or secondary amino group as appropriate.

- 5 A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide, a substituted (1-6C)alkyl chloride, bromide or iodide, or a substituted (1-6C)alkyl-tosylate, conveniently in the presence of a
- 10 suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature. An analogous procedure may be used to introduce optionally substituted (2-6C)alkenyloxy, (2-6C)alkenylamino, (2-6C)alkynloxy or (2-6C)alkynylamino groups into Q¹, R¹ or Q².
- 15 Process (h) For the production of those compounds of the Formula I wherein Q¹, R¹ or Q² contains an amino-hydroxy-disubstituted (1-6C)alkoxy group (such as 2-hydroxy-3-piperidinopropoxy, 2-hydroxy-3-methylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy or 3-[N-(3-dimethylaminopropyl)-N-methylamino]-2-hydroxypropoxy), the reaction of a
- 20 compound of the Formula I wherein Q¹, R¹ or Q² contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

- 25 Process (i) The reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a quinazoline of the Formula XII



XII

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wherein L^1 is a displaceable group as defined hereinbefore and m, R^1 , R^2 , R^3 and Q^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula



- 5 wherein Q^1 and Z have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction is conveniently carried out in the presence of a suitable base, such as an alkali metal hydride, for example sodium hydride.

- 10 The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 50°C.

The compound of Formula XII may be prepared using an analogous procedure to that described for the preparation of Formula VIII, except that the 5-fluoro atom is replaced by L^1 .

- 15 Process (j) For the production of those compounds of the Formula I wherein Q^1 , R^1 or Q^2 contains an amino-substituted (1-6C)alkoxy group (such as 3-piperidinopropoxy, 3-methylaminopropoxy or 3-dimethylaminopropoxy), the reaction of a compound of the Formula I wherein Q^1 , R^1 or Q^2 contains a halogeno-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

- 20 The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

Process (k) For the production of those compounds of the Formula I wherein a heterocyclyl group in R^1 , Q^1 or Q^3 contains an S- or N-oxide the oxidation of a ring N or S atom in a

- 25 compound of the Formula (I). Suitable oxidizing agents include, for example, a peracid (such as m-chloroperbenzoic acid) or perphthalic acid. The oxidation is conveniently carried out in a suitable inert solvent or diluent (such as dichloromethane) at a suitable temperature (such as -5 to 50°C).

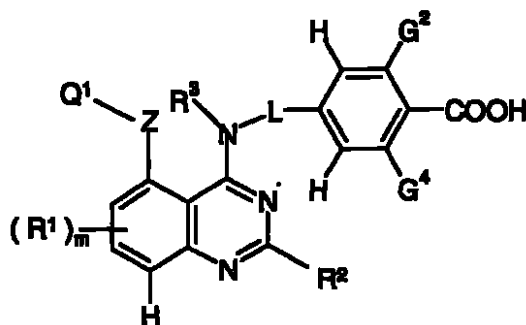
- Process (l) For the production of those compounds of the formula I wherein Q^2 is a group of the formula 1a as hereinbefore defined and :

(i) G^3 is a group of the formula $CON(R^{20})Q^{10}$ wherein R^{20} and Q^{10} are as hereinbefore defined, or

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(ii) G^3 is a group of the formula COQ^{10} and Q^{10} is a nitrogen linked heterocyclyl group,

the coupling of the corresponding carboxy substituted quinazoline of the formula XIII



XIII

- 5 or a reactive derivative thereof, with an amine of the formula $NH(R^{20})Q^{10}$ or $Q^{10}H$ (when Q^{10} is a nitrogen containing heterocyclyl group, for example homopiperidine) as appropriate, wherein R^1 , R^2 , R^3 , R^{20} , Q^1 , Q^{10} , Z , L , m , G^2 and G^4 are as hereinbefore defined except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means. The coupling reaction is conveniently carried out in the
- 10 presence of a suitable coupling agent, such as a carbodimide, or a suitable peptide coupling agent, for example O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate. The coupling reaction is conveniently carried out in an inert solvent such as 1-methyl-2-pyrrolidinone, preferably in the presence of a suitable base, such as an organic amine, for example di-isopropylethylamine.
- 15 By 'reactive derivative' of a compound by the formula XI is meant a derivative of carboxylic acid of formula XI that will react with the amine to give the corresponding amide. Such reactive derivatives include, for example, an acid chloride of the compound of formula XI.

The compound of formula XIII may be prepared using process (a) above by reacting a

20 compound of the formula II with an appropriate carboxy-substituted aniline.

Process (m) For the production of those compounds of the formula I wherein G^3 in Q^2 is a group of the formula OQ^{10} wherein Q^{10} is aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, or heteroaryl, the reaction of compound of formula I wherein G^3 in Q^2 is OH with a compound of the formula $Q^{10}-L^1$, wherein L^1 is a displaceable group, and Q^{10} is as hereinbefore defined

25 except any functional group is protected if necessary, and whereafter any protecting group that is present is removed by conventional means. Suitable displaceable groups are, for example halogens such as chloro, or alkane sulphonyloxy, such as mesyloxy. The reaction is

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conveniently carried out in an inert solvent such as or a dipolar aprotic solvent for example N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out in the presence of a suitable base, such as an alkali metal carbonate, for example potassium carbonate. Generally the
5 reaction is performed at a temperature of from -10 to 120°C, conveniently at or near ambient temperature.

Process (n) For the production of those compounds of the formula I wherein any of Q¹, R¹ or Q² contains an (2-6C)alkanoylamino, substituted (2-6C)alkanoylamino group, the acylation of a quinazoline derivative of the formula I wherein Q¹, R¹ or Q² contains an amino group. A
10 suitable acylating agent is, for example, any agent known in the art for the acylation of amino to acylamino, for example an acyl halide, for example a (2-6C)alkanoyl chloride or bromide, conveniently in the presence of a suitable base, as defined hereinbefore, an alkanolic acid anhydride or mixed anhydride, for example a (2-6C)alkanoic acid anhydride such as acetic : anhydride or the mixed anhydride formed by the reaction of an alkanolic acid and a (1-
15 4C)alkoxycarbonyl halide, for example a (1-4C)alkoxycarbonyl chloride, in the presence of a suitable base as defined hereinbefore. In general the acylation is carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature, in the range, for example, - 30°C to 120°C, conveniently at or near ambient temperature.

An analogous process may be used to prepare compounds of the formula I wherein (1-
20 6C)alkanesulphonylamino group or substituted alkane sulphonylamino group except the corresponding (1-6C)alkanesulphonylhalide or substituted alkane sulphonylhalide (for example methanesulphonyl chloride) is used in place of the acylhalide.

Process (o) For the production of those compounds of the Formula I wherein R¹, Q¹ or Q² contains an (1-6C)alkylamino or substituted (1-6C)alkylamino group or a nitrogen linked
25 heterocyclyl group, the reductive amination of an aldehyde or ketone group in a compound of formula 1, with a (1-6C)alkylamine, substituted (1-6C)alkylamine group or a heterocycle containing an NH group in the presence of a suitable reducing agent. A suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride, formic acid or, preferably, an alkali metal
30 borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxymethylborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran or diethyl ether for the more powerful reducing agents such as lithium

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aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride and sodium cyanoborohydride. The reaction is conveniently performed at a temperature in the range, for example, 10 to 100°C, conveniently at or near ambient temperature.

5 An analogous reductive amination to that described above may be used to introduce an alkyl or substituted alkyl group onto a primary or secondary amine group in a compound of the formula I by reductive amination with a corresponding ketone in the presence of a suitable reducing agent. For example, for the production of those compounds of the Formula I wherein Q¹ or Q² contains a N-methyl group, the corresponding compound containing an NH
10 group may be reacted with formaldehyde in the presence of a suitable reducing agent as described above.

Process (p) The conversion of one compound of the Formula I into another compound of the Formula I

It will be appreciated that certain of the various ring substituents in the compounds of
15 the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above (for example as in process (r)), and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction,
20 reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the
25 introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl; the substitution of an NH group in Q¹ or Q² by the reaction with an optionally substituted alkyl halide, an optionally substituted alkenyl halide, an optionally substituted
30 alkynyl halide or optionally substituted alkanoyl halide; the introduction of a halogeno group into an aromatic or heteroaromatic ring (for example within an indole) by reaction with an N-

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halogeno-succinimide; and the introduction of a cyano group into an aromatic ring by reaction with an isocyanate, for example chlorosulphonyl isocyanate.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of
5 said quinazoline derivative with a suitable acid using a conventional procedure.

Biological Assays

The inhibitory activities of compounds were assessed in non-cell based protein tyrosine kinase assays as well as in cell based proliferation assays before their *in vivo* activity was assessed in Xenograft studies.

10 a) Protein Tyrosine Kinase phosphorylation Assays

This test measures the ability of a test compound to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by an enzyme selected from the EGFR kinase, erbB2 kinase and erb4 kinase.

Recombinant intracellular fragments of EGFR, erbB2 and erbB4 (accession numbers
15 X00588, X03363 and L07868 respectively) were cloned and expressed in the baculovirus/Sf21 system. Lysates were prepared from these cells by treatment with ice-cold lysis buffer (20mM N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid (HEPES) pH7.5, 150mM NaCl, 10% glycerol, 1% Triton X-100, 1.5mM MgCl₂, 1mM ethylene glycol-bis(β-aminoethyl ether) N',N',N',N'-tetraacetic acid (EGTA), plus protease inhibitors
20 and then cleared by centrifugation.

Constitutive kinase activity of these recombinant proteins was determined by their ability to phosphorylate a synthetic peptide (made up of a random co-polymer of Glutamic Acid, Alanine and Tyrosine in the ratio of 6:3:1). Specifically, Maxisorb™ 96-well immunoplates were coated with synthetic peptide (0.2μg of peptide in a 200μl phosphate
25 buffered saline (PBS) solution and incubated at 4°C overnight). Plates were washed in 50mM HEPES pH 7.4 at room temperature to remove any excess unbound synthetic peptide. EGFR, erbB2 or erbB4 activities were assessed by incubation in peptide coated plates for 20 minutes at room temperature in 100mM HEPES pH 7.4 at room temperature, adenosine triphosphate (ATP) at Km concentration for the respective enzyme, 10mM MnCl₂, 0.1mM Na₃VO₄,
30 0.2mM DL-dithiothreitol (DTT), 0.1% Triton X-100 with test compound in DMSO (final concentration of 2.5%). Reactions were terminated by the removal of the liquid components

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of the assay followed by washing of the plates with PBS-T (phosphate buffered saline with 0.5% Tween 20).

The immobilised phospho-peptide product of the reaction was detected by immunological methods. Firstly, plates were incubated for 90 minutes at room temperature with anti-phosphotyrosine primary antibodies that were raised in the mouse (4G10 from Upstate Biotechnology). Following extensive washing, plates were treated with Horseradish Peroxidase (HRP) conjugated sheep anti-mouse secondary antibody (NXA931 from Amersham) for 60 minutes at room temperature. After further washing, HRP activity in each well of the plate was measured colorimetrically using 22'-Azino-di-[3-ethylbenzthiazoline sulphate (6)] diammonium salt crystals (ABTS™ from Roche) as a substrate.

Quantification of colour development and thus enzyme activity was achieved by the measurement of absorbance at 405nm on a Molecular Devices ThermoMax microplate reader. Kinase inhibition for a given compound was expressed as an IC₅₀ value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of phosphorylation in this assay. The range of phosphorylation was calculated from the positive (vehicle plus ATP) and negative (vehicle minus ATP) control values.

b) KB cell proliferation assay

This assay measures the ability of a test compound to inhibit the proliferation of KB cells (human naso-pharyngeal carcinoma obtained from the American Type Culture Collection (ATCC)).

KB cells (human naso-pharyngeal carcinoma obtained from the ATCC) were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% foetal calf serum, 2 mM glutamine and non-essential amino acids at 37°C in a 7.5% CO₂ air incubator. Cells were harvested from the stock flasks using Trypsin/ethylenediaminetetraacetic acid (EDTA). Cell density was measured using a haemocytometer and viability was calculated using trypan blue solution before being seeded at a density of 1.25×10^3 cells per well of a 96 well plate in DMEM containing 2.5% charcoal stripped serum, 1mM glutamine and non-essential amino acids at 37°C in 7.5% CO₂ and allowed to settle for 4 hours.

Following adhesion to the plate, the cells are treated with or without EGF (final concentration of 1ng/ml) and with or without compound at a range of concentrations in dimethylsulphoxide (DMSO) (1% final) before incubation for 4 days. Following the incubation period, cell numbers were determined by removal of the media by aspiration and

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incubating with 50µl of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (stock 5mg/ml) for 2 hours. MTT solution was then removed by aspiration, allowed to air dry and the cells dissolved upon the addition of 100µl of DMSO.

Absorbance of this solubilised cells was read at 540nm to quantify cell biomass.

- 5 Inhibition of proliferation was expressed as an IC₅₀ value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of proliferation. The range of proliferation was calculated from the positive (vehicle plus EGF) and negative (vehicle minus EGF) control values.

c) H16N-2 cell proliferation assay

- 10 This assay measures the ability of a test compound to inhibit heregulin β or EGF driven proliferation of H16N-2 cells. These non-neoplastic epithelial cells respond in a proliferative manner to stimulation with either EGF or heregulin β (Ram, G.R. and Ethier, S.P. (1996) *Cell Growth and Differentiation*, 7, 551-561) were isolated human mammary tissue (Band, V. and Sager, R. Tumour progression in breast cancer. In: J. S. Rhim and A. Ditschilo (eds.), *Neoplastic Transformation in human Cell Culture*, pp 169-178. Clifton, NJ: Humana Press, 1991) and were obtained from the Dana-Farber Cancer Institute, 44 Binney Street, Boston, Massachusetts 02115.

- H16N-2 cells were routinely cultured in culture medium (a 1:1 mix of Gibco F12 and Ham's αMEM media containing 1 % foetal calf serum, 10mM HEPES, 1µg/ml Insulin, 20 12.5ng/ml EGF, 2.8µM Hydrocortisone, 2nM Estradiol 5µM Ascorbic Acid, 10µg/ml Transferrin, 0.1mM Phosphoethanolamine, 15nM Sodium Selenite, 2mM Glutamine, 10nM Tri-iodo-thyrone, 35µg/ml Bovine pituitary Extract and 0.1mM Ethanolamine) at 37°C in a 7.5% CO₂ air incubator. Cells were harvested from the stock flasks using Trypsin/ethylenediaminetetraacetic acid (EDTA). Cell density was measured using a 25 haemocytometer and viability was calculated using trypan blue solution before being seeded at a density of 1.0x10³ cells per well of a 96 well plate in the above media at 37°C in 7.5% CO₂ and allowed to settle for 72 hours.

- Following this, the cells were starved of serum for 24 hours upon the addition of starvation medium (a 1:1 mix of Gibco F12 and Ham's αMEM media containing, 10mM 30 HEPES, 2nM Estradiol, 5µM Ascorbic Acid, 10µg/ml Transferrin, 0.1mM Phosphoethanolamine, 15nM Sodium Selenite, 2mM Glutamine, and 0.1mM Ethanolamine) and incubated at 37°C in 7.5% CO₂. The cells were then treated with or without compound at

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a range of concentrations in dimethylsulphoxide (DMSO) (1% final) for two hours before the addition of exogenous ligand (at a final concentration of 100ng/ml of heregulin β or 5ng/ml of EGF) and incubation with both ligand and compound for 4 days at 37°C in 7.5% CO₂.

Following the incubation period, cell numbers were determined by removal of the media by aspiration and incubating with 50 μ l of 3-(4,5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) (stock 5mg/ml) for 2 hours. MTT solution was then removed by aspiration, allowed to air dry and the cells dissolved upon the addition of 100 μ l of DMSO.

Absorbance of this solubilised cells was read at 540nm to quantify cell biomass.

Inhibition of proliferation was expressed as an IC₅₀ value. This was determined by calculation of the concentration of compound that was required to give 50% inhibition of proliferation. The range of proliferation was calculated from the positive (vehicle plus ligand) and negative (vehicle minus ligand) control values.

d) *In vivo* LoVo Xenograft assay

This assay measures the ability of a test compound to inhibit the growth of a LoVo tumour cell xenograft (colorectal adenocarcinoma obtained from the ATCC) in Female Swiss athymic mice (Alderley Park, *nu/nu* genotype).

Female Swiss athymic (*nu/nu* genotype) mice were bred and maintained in Alderley Park in negative pressure Isolators (PFI Systems Ltd.). Mice were housed in a barrier facility with 12hr light/dark cycles and provided with sterilised food and water *ad libitum*. All procedures were performed on mice of at least 8 weeks of age. LoVo tumour cell xenografts were established in the hind flank of donor mice by sub-cutaneous injections of 1x10⁷ freshly cultured cells in 100 μ l of serum free media per animal. On day 5 post-implant, mice were randomised into groups of 7 prior to the treatment with compound or vehicle control that was administered once daily at 0.1ml/kg body weight. Tumour volume was assessed twice weekly by bilateral Vernier calliper measurement, using the formula (length x width) x $\sqrt{(\text{length} \times \text{width}) \times (\pi/6)}$, where length was the longest diameter across the tumour, and width was the corresponding perpendicular. Growth inhibition from start of treatment was calculated by comparison of the mean changes in tumour volume for the control and treated groups, and statistical significance between the two groups was evaluated using a Student's *t* test.

e) *In vivo* BT-474 Xenograft assay

This assay measures the ability of a test compound to inhibit the growth of a BT-474 tumour cell xenograft (human mammary carcinoma obtained from Dr Baselga, Laboratorio

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Recerca Oncologica, Pasco Vall D'Hebron 119-129, Barcelona 08035, Spain) in Female Swiss athymic mice (Alderley Park, *nu/nu* genotype) (Baselga, J. *et al.* (1998) *Cancer Research*, 58, 2825-2831).

Female Swiss athymic (*nu/nu* genotype) mice were bred and maintained in Alderley Park in negative pressure Isolators (PFI Systems Ltd.). Mice were housed in a barrier facility with 12hr light/dark cycles and provided with sterilised food and water *ad libitum*. All procedures were performed on mice of at least 8 weeks of age. BT-474 tumour cell xenografts were established in the hind flank of donor mice by sub-cutaneous injections of 1×10^7 freshly cultured cells in 100 μ l of serum free media with 50% Matrigel per animal. On day 14 post-implant, mice were randomised into groups of 10 prior to the treatment with compound or vehicle control that was administered once daily at 0.1ml/kg body weight. Tumour volume was assessed twice weekly by bilateral Vernier calliper measurement, using the formula (length x width) x $\sqrt{(\text{length} \times \text{width}) \times (\pi/6)}$, where length was the longest diameter across the tumour, and width was the corresponding perpendicular. Growth inhibition from start of treatment was calculated by comparison of the mean changes in tumour volume for the control and treated groups, and statistical significance between the two groups was evaluated using a Students *t* test.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c), (d) and (e):-

- Test (a):- IC_{50} in the range, for example, 0.001 - 10 μ M;
- Test (b):- IC_{50} in the range, for example, 0.001 - 20 μ M;
- Test (c):- IC_{50} in the range, for example, 0.001 - 20 μ M;
- Test (d):- activity in the range, for example, 1-200 mg/kg/day;
- Test (e):- activity in the range, for example, 1-200 mg/kg/day;

No physiologically unacceptable toxicity was observed in Test (d) or (e) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

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According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

5 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for
10 example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended
15 for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral
20 administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the
25 Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to
30 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for

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example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

We have found that the compounds of the present invention possess anti-proliferative properties such as anti-cancer properties that are believed to arise from their erbB family receptor tyrosine kinase inhibitory activity, particularly inhibition of the EGFR and/or erbB2 and/or erbB4 receptor tyrosine kinases. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by erbB receptor tyrosine kinases, i.e. the compounds may be used to produce a receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for the treatment of malignant cells characterised by inhibition of one or more of the erbB family of receptor tyrosine kinases. Particularly the compounds of the invention may be used to produce an anti-proliferative and/or pro-apoptotic and/or anti-invasive effect mediated alone or in part by the inhibition of erbB receptor tyrosine kinases. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours that are sensitive to inhibition of one or more of the erbB receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4 kinase that are involved in the signal transduction steps which drive proliferation and survival of these tumour cells. Accordingly the compounds of the present invention are expected to be useful in the treatment and/or prevention of a number of hyperproliferative disorders by providing an anti-proliferative effect. These disorders include, for example psoriasis, benign prostatic hyperplasia (BPH), atherosclerosis and restenosis and, in particular, EGF and/or erbB2 receptor tyrosine kinase driven tumours. Such benign or malignant tumours may affect any tissue and include non-solid tumours such as leukaemia, multiple myeloma or lymphoma, and also solid tumours, for example bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancers.

Certain compounds according to the present invention possess potent inhibitory activity against EGFR tyrosine kinase whilst possessing less potent activity against other erb receptor tyrosine kinases such as erbB2. Such compounds are expected to be useful as selective receptor tyrosine inhibitors. Furthermore, certain compounds according to the present

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invention are potent inhibitors of both EGFR and erbB2 tyrosine kinases and are expected to be useful in the treatment of conditions mediated by both EGFR and erbB2 tyrosine kinases.

According to this aspect of the invention there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament.

5 Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a
10 method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

According to a further aspect of the invention there is provided a compound of the
15 formula I, or a pharmaceutically acceptable salt thereof, for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or
20 treatment of those tumours which are sensitive to inhibition of erbB receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4, that are involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of
25 one or more of the erbB family of receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4, that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined
30 hereinbefore.

According to a further aspect of the invention there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the erbB family of

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receptor tyrosine kinases, such as EGFR and/or erbB2 and/or erbB4, that are involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells.

According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as
5 defined hereinbefore in the manufacture of a medicament for use in providing a EGFR and/or erbB2 and/or erbB4 kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing a EGFR and/or an erbB2 and/or an erbB4 kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering
10 to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, for use in providing a EGFR and/or an erbB2 and/or an erbB4 kinase inhibitory effect.

15 According to a further aspect of the invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a selective EGFR kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a
20 method for providing a selective EGFR kinase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a compound of the
25 formula I, or a pharmaceutically acceptable salt thereof, for use in providing a selective EGFR kinase inhibitory effect.

By "a selective EGFR kinase inhibitory effect" is meant that the quinazoline derivative of formula I is more potent against EGFR tyrosine kinase than it is against other kinases. In particular the quinazoline derivative of formula I is more potent against EGFR tyrosine kinase
30 than it is against other erbB receptor tyrosine kinases such as erbB2. For example in a cellular assay (such as in the H16N-2 assay described herein) the quinazoline derivative of formula I is at least 5 times, preferably at least 10 times more potent against EGFR tyrosine kinase driven

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proliferation than it is against erbB2 receptor tyrosine kinase driven proliferation, as determined from the relative IC₅₀ values

According to a further aspect of the present invention there is provided the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as
5 defined hereinbefore in the manufacture of a medicament for use in the treatment of a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer.

According to a further feature of this aspect of the invention there is provided a
10 method for treating a cancer selected from selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer in a warm-blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a
15 quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a compound of the formula I, or a pharmaceutically acceptable salt thereof, for use in the treatment of a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS,
20 breast, colorectal, endometrial, gastric, head and neck, hepatic, lung, neuronal, oesophageal, ovarian, pancreatic, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer.

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the
25 following categories of anti-tumour agents :-

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed,
30 methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and

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taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, ansacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;

(iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) other inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [HerceptinTM] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [AvastinTM], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

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- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or
- 5 radiotherapy such as multi-drug resistance gene therapy; and
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as
- 10 cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and

15 the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents

20 for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of the erbB receptor tyrosine protein kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, and in the search for new pharmacological agents.

25 The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise:

- (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;
- (ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent
- 30 was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;
- (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

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- (iv) in general, the course of reactions was followed by TLC and / or analytical LC-MS, and reaction times are given for illustration only;
- (v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;
- 5 (vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
- (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO- d_6) as solvent unless
- 10 otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad;
- (viii) chemical symbols have their usual meanings; SI units and symbols are used;
- (ix) solvent ratios are given in volume:volume (v/v) terms; and
- (x) mass spectra were run with an electron energy of 70 electron volts in the chemical
- 15 ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(MH)^+$ which refers to the protonated mass ion; reference to M^+ is to the mass ion generated by loss of an electron; and reference to $M-H^+$ is to
- 20 the mass ion generated by loss of a proton;
- (xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulphur atom have not been resolved;
- (xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;
- 25 (xvi) the following abbreviations have been used:

THF	tetrahydrofuran;
DMF	<i>N,N</i> -dimethylformamide;
DMA	<i>N,N</i> -dimethylacetamide;
NMP	1-methyl-2-pyrrolidinone;
30 DCM	dichloromethane;
DMSO	dimethylsulphoxide;
HATU	O-(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -Tetramethyluronium Hexafluoro-Phosphate;

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<i>m</i> -CPBA	<i>Meta</i> -Chloroperbenzoic acid;
IPA	isopropanol; and
ether	diethyl ether.

xvii) where a synthesis is described as leading to an acid addition salt (e.g. HCl salt), the
5 stoichiometry of the salt was not determined. Unless otherwise stated, all NMR data is
reported on free-base material, with isolated salts converted to the free-base form prior to
characterisation by treating a solution of the salt in aqueous methanol with a base such as
ammonium hydroxide or sodium bicarbonate thereby precipitating the free base, or by
chromatography on silica using an eluant containing a base such as ammonia. Alternatively
10 the free base may be obtained by an extraction method wherein the compound is partitioned
between an organic solvent and a basic aqueous medium. The free base is then isolated from
the organic medium by, for example evaporation of the organic solvent.

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Example 1**4-(3-Bromoanilino)-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

A mixture of 4-chloro-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16) (0.2 g), 3-bromoaniline (0.066 ml) and HCl in dioxane (4M, 0.5 ml) in IPA (3 ml) was heated at reflux for 6 hours. The reaction was cooled, and the resulting precipitate filtered, washed with IPA and ether, and dried *in vacuo* to yield the title compound as a yellow solid (0.115 g, 43%); Mass spectrum M^+ 527, 525.

The procedure described above was repeated using the appropriate 4-chloroquinazoline and aniline. Thus were obtained the compounds described below:

Example 1.1**4-(3-Chloroanilino)-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16) with 3-chloroaniline in 53% yield; Mass spectrum M^+ 481.

Example 1.2**4-(3-Methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) with *meta*-toluidine in 25% yield; Mass spectrum MH^+ 349.

Example 1.3**4-(3-Chloroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) with 3-chloroaniline in 29% yield; Mass spectrum M^+ 369.

Example 1.4**4-(3-Bromoanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) with 3-bromoaniline in 36% yield; Mass spectrum M^+ 415, 413.

Example 1.5**4-(3-Ethynylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) with 3-ethynylaniline in 27% yield; Mass spectrum $M-H^+$ 357.

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Example 1.6**4-(3-Fluoroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) with 3-fluoroaniline in 26% yield; Mass spectrum MH^+ 353.

5 Example 1.7**4-(Indol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) with 5-aminoindole in 30% yield; Mass spectrum MH^+ 374.

Example 1.8**10 4-(Indazol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) with 5-aminoindazole in 30% yield; Mass spectrum MH^+ 375.

Example 1.9**15 4-(3-Chloro-4-(azepan-1-ylcarbonyl)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) with 4-(azepan-1-ylcarbonyl)-3-chloroaniline (reference example 29) in 45% yield; NMR Spectrum ($CDCl_3$) 1.50 (bs, 6H), 1.84 (bs, 2H), 1.99 (m, 2H), 2.30 (m, 4H), 2.34 (s, 3H), 2.81 (m, 2H), 3.31 (m, 2H), 3.72 (m, 2H), 3.92 (s, 3H), 4.57 (m, 1H),
20 6.52 (d, 1H), 6.85 (d, 1H), 7.24 (d, 1H), 7.56 (dd, 1H), 8.09 (d, 1H), 8.61 (s, 1H), 9.99 (s, 1H);
Mass Spectrum MH^+ 524.

Example 1.10**4-(3-Bromoindol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

25 Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 5-amino-3-bromoindole (reference example 25.2) in 19% yield; NMR Spectrum ($CDCl_3$) 2.06 (m, 2H), 2.22 (m, 2H), 2.33 (s, 3H), 2.40 (m, 2H), 2.75 (m, 2H), 3.92 (s, 3H), 4.65 (m, 1H), 6.51 (d, 1H), 6.83 (d, 1H), 7.22 (d, 1H), 7.35 (d, 1H), 7.47 (dd, 1H), 7.84 (s, 1H), 8.47 (bs, 1H), 8.53 (s, 1H), 9.84 (s, 1H); Mass Spectrum MH^+
30 482, 484.

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Example 1.11**4-(3-Chloroindol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) and 5-amino-3-chloroindole (reference example 26.2) in 11% yield; Mass

5 Spectrum M^+ 408.

Example 1.12**4-(3-Cyanoindol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) with 5-aminoindole-3-carbonitrile (reference example 27.2) in 28% yield;

10 NMR spectrum (DMSO- d_6) 2.3 (m, 4H), 2.7 (m, 3H), 3.2 - 3.6 (m, 4H) 5.1 (m, 1H), 7.5 (m, 3H), 7.7 (m, 1H), 8.0 (m, 1H), 8.2 (s, 1H), 8.3 (s, 1H), 8.9 (s, 1H); Mass spectrum MH^+ 399.

Example 2**4-(3-Bromoanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

A solution of hydrochloric acid in dioxane (4M, 0.5 ml) was added to a mixture of 4-
15 chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) (308 mg) and 3-bromoaniline (172 mg) in dioxane (20 ml). The resulting suspension was heated at reflux for 4 hours, then allowed to cool to room temperature. The reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate solution and DCM. Combined organic extracts were dried (sodium sulphate) and concentrated to give an orange
20 oil, which was purified by chromatography using 0-5% methanol in DCM as eluent to give the title compound as a white solid (190 mg, 43%); NMR Spectrum ($CDCl_3$) 2.10 (m, 2H), 2.38 (m, 4H), 2.42 (s, 3H), 2.90 (m, 2H), 4.00 (s, 3H), 4.66 (m, 1H), 6.60 (d, 1H), 6.93 (d, 1H), 7.31 (m, 2H), 7.65 (m, 1H), 8.22 (m, 1H), 8.68 (s, 1H), 9.98 (s, 1H); Mass Spectrum MH^+ 443, 445.

25 The procedure described above was repeated using the appropriate 4-chloroquinazoline and aniline. Thus were obtained the compounds described below:

Example 2.1**4-(3-Chloroindol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline
30 (reference example 16.2) and 5-amino-3-chloroindole (reference example 26.2) in 51% yield; NMR Spectrum (DMSO- d_6) 1.94 (m, 2H), 2.14 (m, 2H), 2.17 (s, 3H), 2.34 (m, 2 H),

2.64 (m, 2H), 3.92 (s, 3H), 4.86 (m, 1H), 6.81 (s, 2H), 7.34 (dd, 1H), 7.47 (d, 1H), 7.55 (d, 1H), 9.97 (s, 1H), 11.37 (s, 1H); Mass Spectrum MH^+ 438, 440.

Example 2.2

4-(3-Ethynylanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

- 5 Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 3-ethynylaniline in 41% yield; NMR Spectrum ($CDCl_3$) 2.10 (m, 2H), 2.28 (m, 4H), 2.35 (s, 3H), 2.83 (m, 2H), 3.10 (s, 1H), 3.93 (s, 3H), 4.59 (m, 1H), 6.53 (d, 1H), 6.85 (d, 1H), 7.24 - 7.36 (m, 2H), 7.76 (d, 1H), 7.94 (d, 1H), 8.59 (s, 1H), 9.90 (s, 1H); Mass Spectrum MH^+ 389.

10 Example 2.3

4-(Indazol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

- Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 5-aminoindazole in 28% yield; NMR Spectrum ($DMSO-d_6$) 1.93 (m, 2H), 2.19 (bs, 4H), 2.32 (t, 2H), 2.63 (m, 2H), 3.91 (s, 3H), 4.84 (m, 1H), 6.82 (s, 2H), 7.52 (d, 1H), 7.59 (d, 1H), 8.10 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H), 13.05 (s, 1H); Mass Spectrum MH^+ 405.

Example 2.4

4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

- Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 3-chloro-4-fluoroaniline in 31% yield; NMR Spectrum ($CDCl_3$) 2.00 (m, 2H), 2.31 (m, 7H), 2.80 (m, 2H), 3.92 (s, 3H), 4.58 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.46 (m, 1H), 8.00 (dd, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Mass Spectrum MH^+ 417, 419.

Example 2.5

25 4-(3-Chloroanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

- Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 3-chloroaniline in 36% yield; NMR Spectrum ($CDCl_3$) 2.01 (m, 2H), 2.30 (m, 7H), 2.81 (m, 2H), 3.92 (s, 3H), 4.57 (m, 1H), 6.52 (d, 1H), 6.85 (d, 1H), 7.08 (m, 1H), 7.28 (t, 1H), 7.51 (dm, 1H), 7.99 (t, 1H), 8.59 (s, 1H), 9.92 (s, 1H); Mass Spectrum MH^+ 399, 401.

Example 2.6

30 7-Methoxy-4-(3-methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

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Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and *meta*-toluidine in 76% yield; NMR Spectrum (CDCl₃) 2.03 (m, 2H), 2.34 (m, 7H), 2.40 (s, 3H), 2.82 (m, 2H), 3.92 (s, 3H), 4.58 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.27 (m, 1H), 7.53 (d, 1H), 7.56 (s, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Mass Spectrum 5 MH⁺ 379.

Example 2.7

4-(3-Fluoroanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 3-fluoroaniline in 41% yield; NMR Spectrum (CDCl₃) 2.01 (m, 2H), 2.28 (m, 4H), 2.33 (s, 3H), 2.83 (m, 2H), 3.92 (s, 3H), 4.57 (m, 1H), 6.52 (d, 1H), 10 6.80 (m, 1H), 6.85 (d, 1H), 7.29 (m, 2H), 7.88 (m, 1H), 8.59 (s, 1H), 9.98 (s, 1H); Mass Spectrum MH⁺ 383.

Example 2.8

4-(Indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 5-aminoindole in 17% yield; NMR Spectrum (CDCl₃) 2.06 (m, 2H), 2.22 - 2.38 (m, 7H), 2.77 (m, 2H), 3.91 (s, 3H), 4.61 (m, 1H), 6.50 (d, 1H), 6.36 (m, 1H), 15 7.22 (t, 1H), 7.38 (s, 2H), 7.96 (s, 1H), 8.25 (bs, 1H), 8.51 (s, 1H), 9.82 (s, 1H); Mass Spectrum MH⁺ 404.

20 Example 2.9

4-(3-Chloro-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 4-amino-2-chlorophenol in 72% yield; NMR spectrum (DMSO-d₆) 1.9 (m, 2H), 2.1 (m, 2H), 2.2 (s, 3H), 2.3 (m, 2H), 2.6 (m, 2H), 3.9 (s, 3H), 4.8 25 (m, 1H) 6.8 (s, 1H), 7.0 (d, 3H), 7.3 (dd, 1H), 8.0 (d, 1H), 8.4 (s, 1H), 9.8 (s, 1H), 10.0 (bs, 1H); Mass spectrum MH⁺ 415.

Example 2.10

4-(3-Methyl-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 4-aminocresol in 84% yield; NMR spectrum (DMSO-d₆) 1.9 30 (m, 2H), 2.1 (m, 2H), 2.2 (s, 3H), 2.2 (s, 3H), 2.3 (m, 2H), 2.6 (m, 2H), 3.9 (s, 3H), 4.8 (m,

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1H) 6.8 (s, 2H), 6.8 (d, 1H), 7.4 (dd, 1H), 7.4 (s, 1H), 8.4 (s, 1H), 9.2 (s, 1H), 9.7 (s, 1H), 10.0 (bs, 1H); Mass spectrum MH⁺ 395.

Example 3

4-(3-Methylbenzothiazol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline

5 hydrochloride

A mixture of 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) (0.42 g) and 5-amino-3-methylbenzothiazole (reference example 27) (0.25 g) in IPA (10 ml) were heated at reflux for 16 hours, then allowed to cool to room temperature. A solid precipitated from the mixture and this was filtered, washed with IPA and diethyl ether, and
10 dried *in vacuo* to give the title compound as a yellow solid (0.4 g, 60%); Mass Spectrum MH⁺ 406.

The procedure described above was repeated using the appropriate aniline and chloroquinazoline. Thus were obtained the compounds described below:

Example 3.1

15 4-(3-Ethynyl 4-(2-fluorobenzyloxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) with 3-ethynyl-4-(2-fluorobenzyloxy)aniline (reference example 42) in 67% yield; Mass Spectrum MH⁺ 514.

20 Example 3.2

4-(3-Ethynyl 4-(3-fluorobenzyloxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) with 3-ethynyl-4-(3-fluorobenzyloxy)aniline (reference example
25 42.1) in 60% yield; Mass Spectrum MH⁺ 514.

Example 3.3

4-(3-Fluoro-4-(1-methyl-1H-imidazol-2-ylthio)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline hydrochloride

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline
30 (reference example 16.2) with 3-fluoro-4-(1-methyl-1H-imidazol-2-ylthio)aniline (reference example 26.3) in 54% yield; NMR spectrum (DMSO-d₆, 373K) 1.9 - 2.0 (m, 2H), 2.1 - 2.2 (m, 2H), 2.25 (s, 3H), 2.25 - 2.35 (m, 2H), 2.6 - 2.7 (m, 2H), 3.7 (s, 3H), 3.9 (s, 3H), 4.7 - 4.8

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(m, 1H), 6.8 (d, 1H), 6.85 (d, 1H), 7.0 (s, 1H), 7.1 - 7.2 (t, 1H), 7.3 (s, 1H), 7.3 - 7.4 (dd, 1H), 8.0 - 8.1 (d, 1H), 8.5 (s, 1H), 10.0 (bs, 1H); Mass Spectrum MH^+ 495.

Example 4

4-(3-Bromoindazol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline

5 Di-*iso*-propylethylamine (94 μ l) was added to a mixture of 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) (75 mg) and 5-amino-3-bromoindazole (reference example 25) (115 mg) in IPA (12 ml). The resulting suspension was heated at reflux for 2 hours, then allowed to cool to room temperature. A solid precipitated from the mixture and this was filtered, washed with IPA and diethyl ether, and
10 dried *in vacuo* to afford the title compound as a white solid (114 mg, 93%); NMR Spectrum (DMSO- d_6) 1.97 (m, 2H), 2.20 (m, 5H), 2.38 (m, 2H), 2.70 (m, 2H), 4.82 (m, 1H), 7.20 (d, 1H), 7.37 (d, 1H), 7.57-7.74 (m, 3H), 8.15 (s, 1H), 8.51 (s, 1H), 10.10 (s, 1H), 13.10 (bs, 1H); Mass Spectrum MH^+ 453, 455.

The procedure described above was repeated using the appropriate 4-
15 chloroquinazoline and aniline. Thus were obtained the compounds described below:

Example 4.1

4-(3-Chloroindazol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) and 5-amino-3-chloroindazole (reference example 25.1) in 85% yield; NMR
20 Spectrum (DMSO- d_6) 1.96 (m, 2H), 2.18 (m, 2H), 2.25 (s, 3H), 2.41 (m, 2H), 2.74 (m, 2H), 4.82 (m, 1H), 7.23 (d, 1H), 7.33 (d, 1H), 7.51 - 7.74 (m, 3H), 8.39 (s, 1H), 8.53 (s, 1H), 10.21 (s, 1H), 13.29 (bs, 1H); Mass spectrum MH^+ 409.

Example 4.2

4-(3-Chloro-1-(2-pyridylmethyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 5-amino-3-chloro-1-(2-pyridylmethyl)indole (reference example 26) in 10% yield; NMR Spectrum (CDCl₃) 2.03 (m, 2H), 2.22 (m, 2H), 2.32 (s, 3H), 2.37 (m, 2H), 2.75 (m, 2H), 3.91 (s, 3H), 4.61 (m, 1H), 5.39 (s, 2H), 6.50 (d, 1H), 6.82 (m,
30 2H), 7.18 (m, 2H), 7.27 (d, 1H), 7.44 (dd, 1H), 7.56 (dt, 1H), 7.95 (d, 1H), 8.52 (s, 1H), 8.59 (d, 1H), 9.83 (s, 1H); Mass Spectrum MH^+ 529.

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Example 4.3**4-(3-Chloro-1-(2-pyridylmethyl)indazol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 5-amino-3-chloro-1-(2-pyridylmethyl)indazole (reference example 26.1) in 9% yield; NMR Spectrum (CDCl₃) 2.03 (m, 2H), 2.25 (m, 2H), 2.32 (s, 3H), 2.37 (m, 2H), 2.77 (m, 2H), 3.92 (s, 3H), 4.60 (m, 1H), 5.66 (s, 2H), 6.51 (d, 1H), 6.84 (d, 1H), 6.98 (d, 1H), 7.19 (dd, 2H), 7.39 (d, 1H), 7.58 (m, 2H), 8.13 (d, 1H), 8.55 (s, 1H), 8.58 (d, 1H), 9.88 (s, 1H); Mass Spectrum MH⁺ 530.

10 Example 4.4**7-Methoxy-4-(3-methyl-4-(2-pyridylmethoxy)anilino)-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and 3-methyl-4-(2-pyridylmethoxy)aniline (obtained using the method of Example 13 of WO 96/15118) in 18% yield; NMR Spectrum (CDCl₃) 2.02 (m, 2H), 2.25 (m, 2H), 2.32 (s, 3H), 2.38 (s, 3H), 2.76 (m, 2H), 3.90 (s, 3H), 4.58 (m, 1H), 5.23 (s, 2H), 6.48 (d, 1H), 6.81 (d, 1H), 7.22 (dd, 1H), 7.44 (m, 2H), 7.56 (d, 1H), 7.23 (dt, 1H), 8.50 (s, 1H), 8.59 (d, 1H), 9.65 (s, 1H); Mass Spectrum MH⁺ 486.

Example 4.5**20 4-(3-Methylindol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) and 3-methylindol-5-ylamine (reference example 27.1) in 10% yield; NMR spectrum (DMSO-d₆) 2.2 - 2.4 (m, 5H), 2.8 (s, 3H), 3.2 - 3.7 (m, 6H), 5.1 (m, 1H), 7.2 (s, 1H), 7.3 - 7.6 (m, 4H), 7.8 - 8.0 (m, 2H), 8.8 (d, 1H); Mass spectrum MH⁺ 388.

25 Example 4.6**4-(3-Chloro-4-hydroxyanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) and 3-chloro-4-hydroxyaniline in 60% yield; NMR spectrum (DMSO-d₆) 1.9 (m, 2H), 2.1 (m, 5H), 2.3 (m, 2H), 2.6 (m, 2H), 4.8 (m, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.3 (m, 2H), 7.7 (m, 1H), 8.0 (d, 1H), 8.4 (s, 1H), 10.0 (s, 1H); Mass spectrum MH⁺ 385.

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Example 5**5-(1-Methylpiperidin-4-yloxy)-4-((1R)-1-Phenylethylamino)quinazoline**

4-Chloro-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.1) (0.3 g), (R)- α -methylbenzylamine (0.28 ml) and di-*iso*-propylethylamine (0.94 ml) were heated at
5 reflux in dioxane (20 ml) for 3 hours. The solution was concentrated *in vacuo* and the residue triturated with ether to give the title compound as a white solid (0.29 g, 74%); Mass spectrum MH^+ 363.

The procedure described above was repeated using the appropriate 4-chloroquinazoline and amine. Thus was obtained the compound described below:

10 **Example 5.1****7-Methoxy-5-(1-methylpiperidin-4-yloxy)-4-((1R)-1-Phenylethylamino)quinazoline**

Obtained by reacting 4-chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 16.2) and (R)- α -methylbenzylamine in 47% yield; Mass Spectrum MH^+ 393.

15 **Example 6****4-(3-Chloro-4-fluoroanilino)-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline**

Di-*iso*-propylethylamine (0.18 ml) was added to 7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)-3,4-dihydroquinazolin-4-one (reference example 14) (50
20 mg) dissolved in anhydrous 1, 2-dichloroethane (5 ml) and the resulting solution cooled to 0°C. POCl₃ (40 μ l) was added dropwise and the reaction heated at 80°C for 3 hours. The reaction mixture was concentrated *in vacuo* to give an orange oil which was used without further purification. 3-Chloro-4-fluoroaniline (20 mg) was added to this oil dissolved in IPA (300 μ l), followed by di-*iso*-propylethylamine (11 μ l). The resulting mixture was heated at
25 80°C for 12 hours to give a yellow precipitate. The reaction mixture was cooled to room temperature, the solid filtered, washed with IPA, then diethyl ether and dried *in vacuo* to afford the title compound as a yellow solid (25 mg, 37%); NMR spectrum (DMSO-d₆, 373K) 2.3 - 2.6 (m, 3H), 2.8 (s, 3H), 2.9 (s, 6H), 3.0 - 3.6 (m, 7H), 3.8 (m, 1H), 3.9 (m, 2H), 4.1 (m, 1H), 5.3 (m, 1H), 6.5 (s, 1H), 6.7 (s, 1H), 7.5 (m, 1H), 7.7 (m, 1H), 8.1 (m, 1H), 8.6 (s, 1H),
30 10.1 (m, 1H); Mass spectrum MH^+ 499.

The procedure described above was repeated using the appropriate 3,4-dihydroquinazolin-4-one and aniline. Thus were obtained the compounds described below:

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170**Example 6.1****4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 7-methoxy-5-(tetrahydrofuran-3-yloxy)-3,4-dihydroquinazolin-4-one (reference example 14.1) and 3-chloro-4-fluoroaniline in 44% yield; NMR Spectrum (DMSO-d₆) 2.20 (m, 1H), 2.35 (m, 1H), 3.84 (m, 3H), 3.95 (s, 3H), 4.19 (d, 1H), 5.56 (m, 1H), 7.01 (s, 2H), 7.53 (t, 1H), 7.63 (m, 1H), 8.11 (dd, 1H), 8.81 (s, 1H), 10.41 (s, 1H); Mass spectrum MH⁺ 390.

Example 6.2**4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(tetrahydropyran-4-yloxy)quinazoline**

Obtained by reacting 7-methoxy-5-(tetrahydropyran-4-yloxy)-3,4-dihydroquinazolin-4-one (reference example 14.2) and 3-chloro-4-fluoroaniline in 56% yield; NMR Spectrum (DMSO-d₆) 1.95 (m, 2H), 2.15 (m, 2H), 3.53 (m, 2H), 3.89 (m, 2H), 3.95 (s, 3H), 5.08 (m, 1H), 7.00 (d, 1H), 7.09 (d, 1H), 7.59 (m, 2H), 8.06 (dd, 1H), 8.81 (s, 1H), 10.46 (s, 1H); Mass spectrum MH⁺ 404.

Example 6.3**5-(1-tert-Butoxycarbonylpiperidin-4-yloxy)-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline**

Obtained by reacting 5-(1-tert-butoxycarbonylpiperidin-4-yloxy)-7-methoxy-3,4-dihydroquinazolin-4-one (reference example 15) and 3-chloro-4-fluoroaniline in 54% yield; NMR Spectrum (CDCl₃) 1.48 (s, 9H), 1.86 (m, 2H), 2.24 (m, 2H), 3.20 (m, 2H), 3.92 (s, 3H), 4.00 (m, 2H), 4.69 (m, 1H), 6.53 (d, 1H), 6.87 (d, 1H), 7.14 (t, 1H), 7.39 (m, 1H), 8.02 (dd, 1H), 8.57 (s, 1H), 9.70 (s, 1H); Mass Spectrum MH⁺ 503.

Example 6.4**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)-3,4-dihydroquinazolin-4-one (reference example 14) and 3-chloro-4-(3-fluorobenzoyloxy)aniline (reference example 28) in 61% yield; Mass Spectrum M⁺ 605.

Example 6.5

4-(3-Chloroanilino)-7-(3-(S)-dimethylaminopyrrolidin-1-yl)-5-(tetrahydropyran-4-yloxy)quinazoline

Obtained by reacting 7-(3-(*S*)-dimethylaminopyrrolidin-1-yl)-5-(tetrahydropyran-4-yloxy)-3,4-dihydroquinazolin-4-one (reference example 11.1) and 3-chloroaniline in 73% yield; Mass Spectrum M^+ 468.

Example 7

5 4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(tetrahydrothiophen-3-yloxy)quinazoline

4-(3-Chloro-4-fluoroanilino)-5-hydroxy-7-methoxyquinazoline (reference example 10) (200 mg), triphenylphosphine (247 mg) and 3-hydroxytetrahydrothiophene (98 mg) were dissolved in anhydrous DCM (30 ml) under a nitrogen atmosphere and cooled to 0°C. Di-*tert*-butyl azodicarboxylate (217 mg) in DCM (1 ml) was added dropwise to the reaction, maintaining the internal temperature < 5 °C. The reaction was allowed to warm up to room temperature over 1 hour and then stirred at room temperature for 1 hour. The reaction was concentrated *in vacuo* and the residue purified by chromatography using 1-5% methanol in DCM as eluent to afford the title compound as a white solid (24 mg, 10%); Mass Spectrum MH^+ 404.

15 The procedure described above was repeated using the appropriate 5-hydroxyquinazoline and alcohol. Thus was obtained the compound described below:

Example 7.1

4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(1-*iso*-propylazetidin-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-hydroxy-7-methoxyquinazoline (reference example 10) and 3-hydroxy-1-*iso*-propylazetidine (obtained as described in *J. Org. Chem.*, 1967, 32, 2972-75) in 13% yield; Mass spectrum MH^+ 417.

Example 8

4-(3-Chloro-4-fluoroanilino)-5-(tetrahydrothiopyran-4-yloxy)quinazoline

Sodium hydride (180 mg, 60% dispersion in oil) was added portionwise to 4-hydroxy-25 tetrahydrothiopyran (reference example 36) (320 mg) and 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) (300 mg) in DMF (5 ml) at room temperature. When the foaming had subsided the reaction was heated at 120°C for 2 hours to give a black solution. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography using 1-5% methanol in DCM as eluent to give a colourless oil which 30 crystallised on standing. Diethyl ether was added and the product filtered to afford the title compound as a white solid (235 mg, 65%); NMR Spectrum (DMSO- d_6) 1.82 (m, 1H), 1.98 (m, 3H), 2.53 - 2.71 (m, 2H), 2.98 - 3.01 (m, 1H), 3.15 (m, 1H), 5.03 (m, 1H), 7.22 (d, 1H),

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7.35 (d, 1H), 7.43 (t, 1H), 7.71 (m, 2H), 8.22 (dd, 1H), 8.53 (s, 1H), 10.32 (s, 1H); Mass spectrum MH^+ 390.

The procedure described above was repeated using the appropriate alcohol and 5-fluoroquinazoline. Thus were obtained the compounds described below:

5 Example 8.1

4-(3-Chloro-4-fluoroanilino)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and 3-hydroxytetrahydrofuran in 72% yield; Mass spectrum MH^+ 360.

10 Example 8.2

4-(3-Chloro-4-fluoroanilino)-5-(tetrahydropyran-4-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and 4-hydroxy-tetrahydropyran in 45% yield; Mass spectrum MH^+ 374.

15 Example 8.3

4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxyquinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and cyclopentanol in 40% yield; Mass spectrum MH^+ 358.

Example 8.4

20 4-(3-Chloro-4-fluoroanilino)-5-(1-methylpyrrolidin-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and 3-hydroxy-1-methylpyrrolidine in 34% yield; Mass spectrum MH^+ 371.

Example 8.5

25 4-(3-Chloro-4-fluoroanilino)-5-(1-iso-propylazetidn-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and 3-hydroxy-1-iso-propylazetidine in 54% yield; Mass spectrum MH^+ 387.

Example 8.6

30 4-(3-Chloro-4-fluoroanilino)-5-(tetrahydrothiophen-3-yloxy)quinazoline

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Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and 3-hydroxytetrahydrothiophene in 66% yield; Mass spectrum MH^+ 376.

Example 8.7

5 4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and 3-hydroxy-1-methylpiperidine in 51% yield; NMR Spectrum (DMSO- d_6) 1.25 (t, 1H), 1.47-1.72 (m, 3H), 2.02 (m, 2H), 2.30 (s, 3H), 2.81 (m, 1H), 3.14 (m, 1H), 5.08 (m, 1H), 7.19 (d, 1H), 7.33 (d, 1H), 7.44 (t, 1H), 7.73 (t, 1H), 8.00 (m, 1H),
10 8.19 (dd, 1H), 8.56 (s, 1H), 10.78 (bs, 1H); Mass spectrum MH^+ 387.

Example 8.8

4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and 4-hydroxy-1-methylpiperidine in 21% yield; Mass spectrum M^+
15 387.

Example 8.9

5-(1-tert-Butoxycarbonylazetidin-3-yloxy)-4-(3-chloro-4-fluoroanilino)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride (reference example 18) and 1-tert-butoxycarbonylazetidin-3-ol (obtained as described in *J.*
20 *Med. Chem.*, (2001), 44(1), 94-104) in 16% yield; NMR spectrum (DMSO- d_6); 1.4 (s, 9H), 4.1 (m, 2H), 4.4 (m, 2H), 5.2 (m, 1H), 6.8 (d, 1H), 7.4 (m, 2H), 7.7 (m, 2H), 8.2 (d, 1H), 8.6 (s, 1H), 9.8 (s, 1H); Mass spectrum MH^+ 445.

Example 9

4-(3-Chloro-4-fluoroanilino)-5-(1,1-dioxo-tetrahydrothiophen-3-yloxy)quinazoline and

25 4-(3-Chloro-4-fluoroanilino)-5-(1-oxo-tetrahydrothiophen-3-yloxy)quinazoline

m-CPBA (240 mg) was added to 4-(3-chloro-4-fluoroanilino)-5-(tetrahydrothiophen-3-yloxy)quinazoline (example 8.6) (192 mg) in DCM (10 ml) at 0°C. The reaction was stirred at this temperature for 30 minutes then concentrated and the residue purified by chromatography using 1-8% methanol in DCM as eluent to afford firstly 4-(3-chloro-4-
30 fluoroanilino)-5-(1,1-dioxo-tetrahydrothiophen-3-yloxy)quinazoline as a beige solid (64.8 mg, 62%); Mass spectrum $M-H^+$ 408; followed by 4-(3-chloro-4-fluoroanilino)-5-(1-

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oxotetrahydrothiophen-3-yloxy)quinazoline as a beige solid (33.4 mg, 33%); Mass spectrum $M-H^+$ 392.

The procedure described above was repeated using the appropriate sulphide. Thus were obtained the compounds described below:

5 Example 9.1

4-(3-Chloro-4-fluoroanilino)-5-((tetrahydrothiopyran-1,1-dioxide)-4-yloxy)quinazoline
and 4-(3-Chloro-4-fluoroanilino)-5-((tetrahydrothiopyran-1-oxide)-4-yloxy)quinazoline

Obtained from 4-(3-chloro-4-fluoroanilino)-5-(tetrahydrothiopyran-4-yloxy)quinazoline (example 8) in 94% yield; Mass spectrum $M-H^+$ 422; and 6% yield; Mass
10 spectrum $M-H^+$ 406, respectively.

Example 10

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

3-Fluorobenzyl chloride (80 mg) was added to a mixture of 4-(3-chloro-4-
15 hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.9) (207 mg) and potassium carbonate (700 mg) in DMF (15 ml). The mixture was stirred vigorously at room temperature for 72 hours, then concentrated *in vacuo*. The resultant oil was partitioned between water and ethyl acetate. The combined organic extracts were then dried (sodium sulphate) and concentrated to give the crude product, which was purified by
20 chromatography using 0-10% methanol in DCM as eluent to give the title compound as a white solid (110 mg, 42%); NMR spectrum ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 4H), 2.3 (s, 3H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.1 (s, 2H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (t, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH^+ 523.

Example 10.1

25 4-(3-Chloro-4-(5-methylisoxazol-3-ylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.9) with 3-chloromethyl-5-methylisoxazole in 60% yield; NMR spectrum ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 4H), 2.3 (s, 3H), 2.4 (s, 3H), 2.8 (m, 2H), 3.9 (s,
30 3H), 4.6 (m, 1H) 5.2 (s, 2H), 6.2 (s, 1H), 6.5 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H), 7.4 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH^+ 510.

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Example 10.2**4-(3-Chloro-4-(thiazol-4-ylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.9) with 4-chloromethylthiazole in 60% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.3 (m, 7H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.4 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H), 7.5 (m, 2H), 7.9 (d, 1H), 8.5 (s, 1H), 8.8 (d, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 512.

Example 10.3**10 4-(3-Chloro-4-(4-pyridylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.9) with 4-picolyl chloride in 45% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.3 (m, 7H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.2 (s, 2H), 6.5 (s, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.4 (d, 2H), 7.5 (d, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 8.6 (d, 2H), 9.8 (s, 1H); Mass spectrum MH⁺ 506.

Example 10.4**4-(3-Chloro-4-benzoyloxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.9) with benzyl chloride in 47% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.3 (m, 7H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H), 7.4 (m, 6H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 505.

Example 10.5**25 4-(3-Chloro-4-(2-cyanobenzoyloxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.9) with 2-chloromethylbenzonitrile in 63% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.3 (m, 7H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.3 (s, 2H), 6.5 (s, 1H), 6.8 (s, 1H), 7.0 (d, 1H), 7.4 (m, 2H), 7.7 (m, 2H), 7.8 (d, 1H), 8.0 (s, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Mass spectrum MH⁺ 530.

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Example 10.6**4-(4-Benzoyloxy-3-methylanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-methyl-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.10) and benzyl chloride in 63% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.2 (m, 2H), 2.3 (s, 3H), 2.3 (s, 3H), 2.4 (m, 2H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.3 - 7.5 (m, 7H), 8.5 (s, 1H), 9.6 (s, 1H); Mass spectrum MH⁺ 485.

Example 10.7**4-(4-(2-Fluorobenzoyloxy)-3-methylanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-methyl-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.9) with 2-fluorobenzyl chloride in 72% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.2 - 2.4 (m, 10H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.2 (s, 2H), 6.5 (s, 1H), 6.8 (s, 1H), 6.9 (d, 1H), 7.1 (m, 2H), 7.3 (m, 1H), 7.5 (m, 3H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 503.

Example 10.8**4-(4-(2,6-Difluorobenzoyloxy)-3-methylanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-methyl-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.10) with 2,6-difluorobenzyl chloride in 81% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.2 (m, 5H), 2.3 (m, 5H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (t, 2H), 7.0 (d, 1H), 7.3 (m, 1H), 7.4 (m, 1H), 7.5 (dd, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 521.

Example 10.9**4-(4-(2-Cyanobenzoyloxy)-3-methylanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-methyl-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.10) with 2-chloromethyl benzonitrile in 83% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.2 (m, 2H), 2.3 (s, 3H), 2.3 (s, 3H), 2.4 (m, 2H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.3 (s, 2H), 6.5 (s, 1H), 6.8 (s, 1H), 6.9 (m, 1H), 7.4 (m, 3H), 7.6 (t, 1H), 7.7 (m, 2H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 510.

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Example 10.10**4-(3-Methyl-4-(5-methylisoxazol-3-ylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-methyl-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.10) with 3-chloromethyl-5-methylisoxazole in 81% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.2 - 2.4 (m, 4H), 2.3 (s, 3H), 2.3 (s, 3H), 2.4 (s, 3H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.1 (s, 2H), 6.1 (s, 1H), 6.5 (s, 1H), 6.8 (s, 1H), 6.9 (m, 1H), 7.5 (m, 2H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 490.

Example 10.11

10 **4-(3-Methyl-4-(thiazol-4-ylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-methyl-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.10) with 4-chloromethylthiazole in 31% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.2 - 2.4 (m, 10H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.3 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.4 - 7.5 (m, 3H), 8.5 (s, 1H), 8.8 (d, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 492.

Example 10.12**4-(4-(3-Fluorobenzoyloxy)-3-methylanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

20 Obtained by reacting 4-(3-methyl-4-hydroxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.10) with 3-fluorobenzyl chloride in 57% yield; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.2 - 2.4 (m, 10H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 - 7.5 (m, 2H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 503.

25 **Example 11**

4-(3-Chloro-4-fluoroanilino)-7-(2-methoxyethoxy)-5-(tetrahydropyran-4-yloxy)quinazoline

Potassium carbonate (0.14 g) and 2-bromoethyl methyl ether (73 µl) were added to a suspension of 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydropyran-4-yloxy)quinazoline trifluoroacetate (reference example 20) in DMF (3 ml). The mixture was stirred at room temperature for 20 hours, then more 2-bromoethyl methyl ether (97 µl) was added and the mixture was stirred at room temperature for a further 20 hours. The mixture

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was then concentrated *in vacuo*, the residue was cooled and cold water was added. The resulting solid was filtered, washed with cold water and dried *in vacuo* to give the title compound as a beige solid (0.09g, 78%); NMR Spectrum (DMSO-d₆) 1.85 (m, 2H), 2.17 (m, 2H), 3.31 (s, 3H), 3.54 (t, 2H), 3.70 (m, 2H), 3.89 (m, 2H), 4.23 (m, 2H), 4.98 (m, 1H), 6.80 (d, 2H), 6.87 (d, 1H), 7.41 (t, 1H), 7.51-7.58 (m, 1H), 8.28 (m, 1H), 8.47 (s, 1H), 9.89 (s, 1H); Mass spectrum MH⁺ 446.

The procedure described above was repeated using the appropriate 7-hydroxyquinazoline and alkyl halide or tosylate. Thus were obtained the compounds described below:

10 Example 11.1

4-(3-Bromoanilino)-7-(2-methoxyethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-(3-bromoanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate (reference example 20.1) and 2-bromoethyl methyl ether in 43% yield; NMR spectrum (DMSO-d₆) 2.2 (m, 2H), 2.4 - 2.6 (m, 7H), 2.7 (m, 2H), 3.3 (s, 3H), 3.7 (m, 2H), 4.2 (m, 2H), 5.0 (m, 1H), 6.9 (dd, 2H), 7.3 (m, 2H), 7.6 (m, 1H), 8.3 (s, 1H), 8.5 (s, 1H); Mass spectrum MH⁺ 489.

Example 11.2

4-(3-Chloro-4-fluoroanilino)-7-(2-methoxyethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydrofuran-3-yloxy)quinazoline trifluoroacetate (reference example 20.2) and 2-bromoethyl methyl ether in 79% yield; NMR Spectrum (DMSO-d₆) 2.16 (m, 1H), 2.32 (m, 1H), 3.32 (s, 3H), 3.71 (m, 2H), 3.78-3.97 (m, 3H), 4.21 (m, 3H), 5.47 (m, 1H), 6.82 (s, 2H), 7.42 (t, 1H), 7.60 (m, 1H), 8.28 (m, 1H), 8.49 (s, 1H), 9.91 (s, 1H); Mass spectrum MH⁺ 434.

25 Example 11.3

4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-(2-methoxyethoxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-5-cyclopentyloxy-7-hydroxyquinazoline trifluoroacetate (reference example 20.3) and 2-bromoethyl methyl ether in 96 % yield; NMR Spectrum (DMSO-d₆) 1.72 (m, 4H), 2.00 (m, 4H), 3.31 (s, 3H), 3.70 (m, 2H), 4.23 (m, 2H), 5.19 (m, 1H), 6.70 (d, 1H), 6.79 (d, 1H), 7.45 (m, 2H), 8.25 (m, 1H), 8.46 (s, 1H), 9.88 (s, 1H); Mass spectrum MH⁺ 432.

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Example 11.4**7-(2-Methoxyethoxy)-4-(3-methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 7-hydroxy-4-(3-methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate (reference example 20.5) and 2-bromoethyl methyl ether in 36% yield; NMR spectrum (DMSO-d₆) 1.8 (m, 2H), 2.1 (m, 5H), 2.3 (m, 5H), 2.6 (m, 2H), 3.3 (s, 3H), 3.7 (m, 2H), 4.2 (m, 2H), 4.8 (m, 1H), 6.8 (m, 2H), 7.0 (m, 1H), 7.2 (m, 1H), 7.5 (m, 1H), 7.6 (s, 1H), 8.4 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 423.

Example 11.5**4-(3-Chloro-4-fluoroanilino)-7-(2-methoxyethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate (reference example 20.4) and 2-bromoethyl methyl ether in 53% yield; NMR spectrum (DMSO-d₆) 1.8 (m, 2H), 2.1 (m, 5H), 2.3 (m, 2H), 2.6 (m, 2H), 3.3 (s, 3H), 3.7 (m, 2H), 4.2 (m, 2H), 4.8 (m, 1H), 6.8 (m, 2H), 7.4 (t, 1H), 7.6 (m, 1H), 8.2 (m, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum M-H⁺ 459.

Example 11.6**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-((1-tert-butoxycarbonyl)piperidin-4-yl)methoxy)quinazoline**

Obtained by reacting *N*-tert-butoxycarbonyl-4-tosyloxymethylpiperidine (reference example 41) and 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-hydroxyquinazoline (reference example 20.8) in 65% yield; NMR spectrum (CDCl₃) 1.3 (m, 2H), 1.5 (s, 9H), 1.8 (m, 2H), 2.0 (m, 3H), 2.2 - 2.4 (m, 7H), 2.8 (m, 4H), 3.9 (d, 2H), 4.2 (m, 2H), 4.6 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 706.

Example 11.7**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(2-methoxyethoxy)quinazoline**

Obtained by reacting 2-methoxyethyl bromide and 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-hydroxyquinazoline (reference example 20.8) in 64% yield as a white solid; NMR spectrum (CDCl₃) 2.0 (m, 2H), 2.2 - 2.3 (m, 7H), 2.8 (m, 2H), 3.5 (s, 3H), 3.8 (m, 2H), 4.2 (m, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.6 (d,

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1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 567.

Example 11.8**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(1-tert-butoxycarbonylpiperidin-4-yl)methoxy)quinazoline**

Obtained by reacting *N*-tert-butoxycarbonyl-4-mesyloxymethylpiperidine (reference example 41) and 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-hydroxyquinazoline (reference example 20.9) in 69% yield; NMR spectrum (CDCl₃) 1.3 (m, 2H), 1.5 (s, 9H), 1.8 (m, 2H), 2.0 (m, 3H), 2.2 - 2.3 (m, 2H), 2.8 (m, 2H), 3.6 (m, 2H), 3.9 (d, 2H), 4.0 (dt, 2H), 4.2 (m, 2H), 4.8 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 693.

Example 11.9**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(2-methoxyethoxy)-5-(3-tetrahydrofuran-2-yloxy)quinazoline**

Obtained by reacting 2-bromoethyl methyl ether with 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-7-hydroxy-5-(3-tetrahydrofuran-2-yloxy)quinazoline (125 mg) (reference example 20.10) in 35% yield; Mass spectrum MH⁺ 540.

Example 12**4-(3-Chloroanilino)-7-(1-methylpiperidin-4-ylmethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline**

7-(1-tert-Butoxycarbonylpiperidin-4-ylmethoxy)-4-(3-chloroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 22.1) (50 mg) was heated at 80°C in formic acid (2 ml) and aqueous formaldehyde (1 ml) for 15 hours. The solvent was removed *in vacuo* to give a pink solid. 7N Ammonia in methanol was added and the solvent removed *in vacuo*. Water was added and the solid thus obtained was filtered and dried to afford the title compound as a beige solid; (30 mg, 71%); NMR spectrum (DMSO-d₆) 1.3 (m, 2H), 1.6 - 2.0 (m, 7H), 2.1 (m, 8H), 2.3 (m, 2H), 2.6 (m, 2H), 2.8 (m, 2H), 4.0 (d, 2H), 4.8 (m, 1H), 6.8 (d, 2H), 7.1 (d, 1H), 7.4 (t, 1H), 7.5 (d, 1H), 8.2 (s, 1H), 8.5 (s, 1H), 10.0 (s, 1H); Mass spectrum MH⁺ 496.

The procedure described above was repeated using the appropriate 1-tert-butoxycarbonyl amine. Thus were obtained the compounds described below:



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Example 12.1**4-(3-Chloro-4-fluoroanilino)-7-(1-methylpiperidin-4-ylmethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained from 7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)-4-(3-chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 22) in 35% yield; NMR spectrum (DMSO- d_6) 1.3 (m, 2H), 1.7 (m, 4H), 1.9 (m, 4H), 2.1 (m, 7H), 2.3 (m, 2H), 2.6 (m, 2H), 2.8 (m, 2H), 4.0 (d, 2H), 4.8 (m, 1H), 6.8 (d, 2H), 7.4 (t, 1H), 7.6 (m, 1H), 8.2 (dd, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH^+ 514.

Example 12.2**4-(3-Chloro-4-fluoroanilino)-5-(1-methylazetidin-3-yloxy)quinazoline**

Obtained from 5-(1-*tert*-butoxycarbonylazetidin-3-yloxy)-4-(3-chloro-4-fluoroanilino)quinazoline (example 8.9) in 18% yield; NMR spectrum (DMSO- d_6) 2.3 (s, 3H), 3.3 (m, 2H), 3.8 (m, 2H), 5.1 (m, 1H), 6.9 (d, 1H), 7.4 (m, 2H), 7.7 (m, 2H), 8.3 (d, 1H), 8.6 (s, 1H); Mass spectrum MH^+ 359.

Example 12.3**4-(3-Chloro-4-fluoroanilino)-7-(1-methylpiperidin-4-ylmethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained from 4-(3-chloro-4-fluoroanilino)-7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 22.2) in 94% yield; NMR Spectrum (DMSO- d_6) 1.36 (m, 2H), 1.75 (m, 2H), 1.90 (m, 2H), 2.18 (s, 3H), 2.22 - 2.40 (m, 1H), 2.50 (m, 2H), 2.79 (m, 2H), 3.78 - 3.98 (m, 5H), 4.18 (d, 1H), 5.45 (m, 1H), 6.80 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.40 (m, 1H), 8.52 (s, 1H), 9.87 (s, 1H); Mass spectrum MH^+ 488.

Example 13**4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline**

Trifluoroacetic acid (20 ml) was added to a solid sample of 5-(1-*tert*-butoxycarbonylpiperidin-4-yloxy)-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline (example 6.3) (200 mg), then stirred at room temperature for 10 minutes. The excess trifluoroacetic acid was removed *in vacuo*, then saturated aqueous sodium hydrogen carbonate was carefully added (effervescence). The product was then extracted into DCM, dried over sodium sulphate and concentrated *in vacuo* to give the crude material, which was purified by chromatography using 0-10% methanol in DCM as eluent, to give the title compound as a

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white solid (130 mg, 81%); NMR Spectrum (DMSO-d₆) 1.84 (m, 2H), 2.24 (m, 2H), 2.83 (m, 2H), 2.40 (m, 2H), 3.12 (m, 2H), 3.35 (bs, 1H), 3.92 (s, 3H), 4.91 (m, 1H), 6.85 (d, 1H), 6.87 (d, 1H), 7.47 (t, 1H), 7.59 (m, 1H), 8.28 (dd, 1H), 8.52 (s, 1H), 9.94 (s, 1H); Mass Spectrum MH⁺ 403.

- 5 The procedure described above was repeated using the appropriate *tert*-butoxycarbonyl protected amine. Thus was obtained the compound described below:

Example 13.1

4-(3-Chloro-4-fluoroanilino)-7-(piperidin-4-ylmethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

- 10 Obtained from 4-(3-chloro-4-fluoroanilino)-7-(1-*tert*-butoxycarbonylpiperidin-4-ylmethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 22.2) in 73% yield; NMR Spectrum (DMSO-d₆) 1.48 (m, 2H), 1.95 (m, 2H), 2.02 - 2.20 (m, 2H), 2.30 (m, 1H), 2.92 (m, 2H), 3.30 (m, 2H), 3.78 - 3.98 (m, 3H), 4.03 (d, 2H), 4.19 (d, 1H), 5.45 (m, 1H), 6.80 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.43 (m, 1H), 8.52 (s, 1H), 9.87 (s, 1H);
- 15 Mass spectrum MH⁺ 474.

Example 13.2

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline

- Obtained from 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-((1-*tert*-butoxycarbonylpiperidin-4-yl)methoxy)quinazoline (example 11.6) in 78% yield; NMR spectrum (CDCl₃) 1.3 (m, 2H), 1.8 (m, 2H), 2.0 (m, 3H), 2.2 - 2.4 (m, 7H), 2.6 - 2.8 (m, 4H), 3.2 (m, 2H), 3.9 (d, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H);
- 20 Mass spectrum MH⁺ 606.

25 Example 13.3

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline

- Obtained from 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-((1-*tert*-butoxycarbonylpiperidin-4-yl)methoxy)quinazoline (example 11.8) in 72% yield; NMR spectrum (CDCl₃) 1.3 (m, 2H), 1.8 (m, 2H), 2.0 (m, 3H), 2.3 (m, 2H), 2.7 (m, 2H), 3.1 (m, 2H), 3.6 (m, 2H), 3.9 (d, 2H), 4.1 (m, 2H), 4.7 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H),
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6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH^+ 593.

Example 14

5-(N-Acetylpiiperidin-4-yloxy)-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline

5 Acetyl chloride (0.18 ml) was added to a solution of 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (90 mg) (example 13) and 4-(dimethylamino)pyridine (approximately 1 mg) in pyridine (20 ml). The mixture was then stirred at room temperature for 1 hour, and concentrated *in vacuo*. The residue was dissolved in DCM, and washed with saturated aqueous sodium hydrogen carbonate, aqueous copper (II) sulphate, then water. Drying over sodium sulphate, followed by concentration *in vacuo* gave a yellow viscous oil. Purification by chromatography, using 0-2% methanol in DCM as eluent, gave the title compound as a yellow foam, which was triturated under cold acetonitrile to give the product as a white solid (30 mg, 29%); NMR Spectrum ($CDCl_3$) 1.88 (m, 2H), 2.15 (s, 3H), 2.29 (m, 2H), 3.26 (m, 1H), 3.39 (m, 1H), 3.84 (m, 1H), 3.93 (s, 3H), 4.32 (m, 1H), 4.76
10 (m, 1H), 6.53 (d, 1H), 6.87 (d, 1H), 7.14 (t, 1H), 7.36 (m, 1H), 8.01 (dd, 1H), 8.57 (s, 1H), 9.63 (s, 1H); Mass Spectrum MH^+ 445.

Example 15

4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(1-propylpiperidin-4-yloxy)quinazoline

Sodium triacetoxyborohydride (63 mg) was added to a stirred solution of 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) (100 mg),
20 propionaldehyde (0.18 ml) and acetic acid (0.5 ml) in 1, 2-dichloroethane (10 ml) at room temperature. After 15 minutes, the reaction mixture was diluted with water, and solid potassium carbonate (excess) was added. The resultant mixture was extracted into DCM, dried over sodium sulphate, and concentrated *in vacuo* to give the crude material as a
25 colourless oil, which solidified on addition of diethyl ether. Trituration of this solid with cold methanol gave the title compound as a white powder (110 mg, 100%); NMR Spectrum ($CDCl_3$) 0.92 (t, 3H), 1.53 (m, 2H), 1.98 (m, 2H), 2.25 (m, 6H), 2.87 (m, 2H), 3.91 (s, 3H), 4.57 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.46 (m, 1H), 8.00 (dd, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Mass Spectrum MH^+ 445.

30 The procedure described above was repeated using the appropriate amine and aldehyde. Thus were obtained the compounds described below:

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Example 15.1**5-(1-Ethylpiperidin-4-yloxy)-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline**

Obtained from 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) and acetaldehyde in 80% yield; NMR Spectrum (CDCl₃) 1.11 (t, 3H), 2.00 (m, 2H), 2.31 (m, 4H), 2.46 (q, 2H), 2.88 (m, 2H), 3.91 (s, 3H), 4.58 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.46 (m, 1H), 8.00 (dd, 1H), 8.56 (s, 1H); 9.83 (s, 1H); Mass Spectrum MH⁺ 431.

Example 15.2**4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(1-(2-methoxyethyl)piperidin-4-yloxy)quinazoline**

Obtained from 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) and 2-methoxyacetaldehyde in 68% yield; NMR Spectrum (CDCl₃) 2.03 (m, 2H), 2.25 (m, 2H), 2.39 (m, 2H), 2.62 (t, 2H), 2.93 (m, 2H), 3.36 (s, 3H), 3.52 (t, 2H), 3.91 (s, 3H), 4.57 (m, 1H), 6.50 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.45 (m, 1H), 8.01 (dd, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Mass Spectrum MH⁺ 461.

Example 16**4-(3-Chloro-4-fluoroanilino)-5-(1-(2-propynyl)piperidin-4-yloxy)-7-methoxy-quinazoline**

Propargyl bromide (80% w/w in toluene, 60 mg) was added to a mixture of 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) (100 mg) and potassium carbonate (343 mg) in DMF (15 ml). The reaction mixture was stirred at room temperature for 4 hours, then poured into water. The resultant fine white precipitate was recovered by filtration, then purified by preparative LC-MS, to give the title compound as a white solid (56 mg, 51%); NMR Spectrum (CDCl₃) 2.03 (m, 2H), 2.19 (t, 1H), 2.30 (m, 2H), 2.56 (m, 2H), 2.91 (m, 2H), 3.39 (d, 2H), 3.92 (s, 3H), 4.61 (m, 1H), 6.52 (d, 1H), 6.85 (d, 1H), 7.13 (t, 1H), 7.47 (m, 1H), 8.01 (dd, 1H), 8.56 (s, 1H), 9.80 (s, 1H); Mass Spectrum MH⁺ 441.

The procedure described above was repeated using the appropriate alkyl or alkenyl halide and amine. Thus was obtained the compound described below:

Example 16.1**5-(1-Allylpiperidin-4-yloxy)-4-(3-chloro-4-fluoroanilino)-7-methoxyquinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) with allyl bromide in 45% yield; NMR Spectrum (CDCl₃)

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1.99 (m, 2H), 2.31 (m, 4H), 2.89 (m, 2H), 3.05 (d, 2H), 3.91 (s, 3H), 4.57 (m, 1H), 5.19 (m, 2H), 5.87 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.47 (m, 1H), 7.99 (dd, 1H), 8.56 (s, 1H), 9.82 (s, 1H); Mass Spectrum MH^+ 443.

Example 17

5 Methyl 2-(4-(4-(3-chloro-4-fluoroanilino)-7-methoxyquinazolin-5-yloxy)piperidin-1-yl)acetate

Potassium carbonate (343 mg), methyl chloroacetate (0.036 ml), and 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) (100 mg) in DMF (2 ml) were stirred and heated in a sealed tube to 120°C using a focussed microwave source.

- 10 The mixture was then cooled, poured into water, and extracted into DCM (containing 2% methanol), dried over sodium sulphate and concentrated *in vacuo*. The resultant crude oil was purified by chromatography, using 0-5% methanol in DCM. This gave the title compound as a colourless oil (72 mg, 61%); NMR Spectrum ($CDCl_3$) 2.05 (m, 2H), 2.30 (m, 2H), 2.57 (m, 2H), 2.98 (m, 2H), 3.31 (s, 2H), 3.73 (s, 3H), 3.92 (s, 3H), 4.60 (m, 1H), 6.51 (d, 1H), 6.85 (d, 1H), 7.13 (t, 1H), 7.46 (m, 1H), 8.02 (dd, 1H), 8.56 (s, 1H), 9.79 (s, 1H); Mass Spectrum MH^+ 475.
- 15

The procedure described above was repeated using the appropriate alkyl halide and amine. Thus were obtained the compounds described below:

Example 17.1

20 4-(4-(3-Chloro-4-fluoroanilino)-7-methoxyquinazolin-5-yloxy)piperidin-1-ylmethyl methyl ketone

- Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) with chloromethyl methyl ketone in 44% yield; NMR Spectrum ($CDCl_3$) 2.05 (m, 2H), 2.16 (s, 3H), 2.29 (m, 2H), 2.46 (m, 2H), 2.88 (m, 2H), 3.27 (s, 2H), 3.92 (s, 3H), 4.59 (m, 1H), 6.51 (d, 1H), 6.85 (d, 1H), 7.14 (t, 1H), 7.45 (m, 1H), 8.01 (dd, 1H), 8.57 (s, 1H), 9.79 (s, 1H); Mass Spectrum MH^+ 459.
- 25

Example 17.2

2-(4-(4-(3-Chloro-4-fluoroanilino)-7-methoxyquinazolin-5-yloxy)piperidin-1-yl)acetamide

- 30 Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) with 2-bromoacetamide in 43% yield; NMR Spectrum ($DMSO-d_6$) 1.99 (m, 2H), 2.18 (m, 2H), 2.32 (m, 2H), 2.90 (s, 2H), 3.92 (s, 3H), 4.83 (m,

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1H), 6.84 (s, 2H), 7.10 (bs, 1H), 7.25 (bs, 1H), 7.47 (t, 1H), 7.57 (m, 1H), 8.31 (dd, 1H), 8.51 (s, 1H), 9.95 (s, 1H); Mass Spectrum MH⁺ 460.

Example 18**4-(3-Chloro-4-fluoroanilino)-5-(1-(methanesulphonyl)piperidin-4-yloxy)-7-methoxy-****5 quinazoline**

Methanesulphonyl chloride (42 mg) was added to a stirred solution of 4-(3-chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline (example 13) (100 mg) and triethylamine (55 mg) in DCM (20 ml) at room temperature. After 1 hour, the reaction mixture was diluted with DCM, washed with saturated aqueous sodium hydrogen carbonate, dried over sodium sulphate and concentrated *in vacuo* to give the crude material, which was triturated under methanol to give the title compound as a white solid (85 mg, 71%); NMR Spectrum (CDCl₃) 2.08 (m, 2H), 2.37 (m, 2H), 2.79 (s, 3H), 3.19 (m, 2H), 3.67 (m, 2H), 3.92 (s, 3H), 4.71 (m, 1H), 6.51 (d, 1H), 6.87 (d, 1H), 7.14 (t, 1H), 7.37 (m, 1H), 8.00 (dd, 1H), 8.56 (s, 1H), 9.58 (s, 1H); Mass Spectrum MH⁺ 481.

Example 19**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-(1-methylpiperazin-4-yl)propoxy)-5-cyclopentyloxyquinazoline hydrochloride**

A solution of 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-chloropropoxy)-5-cyclopentyloxyquinazoline (reference example 21.8) (0.15 g) and 1-methylpiperazine (0.18 ml) in NMP (2 ml) was heated at 80°C for 16 hours. The solution was concentrated *in vacuo* and the residue triturated with ether. The resulting solid was filtered to give the title compound as a white solid (30 mg, 18%); Mass Spectrum MH⁺ 620.

The procedure described above was repeated using the appropriate alkyl halide and amine. Thus were obtained the compounds described below:

Example 19.1**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-(N-(2-methoxyethyl)-N-methylamino)propoxy)-5-cyclopentyloxyquinazoline hydrochloride**

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-chloropropoxy)-5-cyclopentyloxyquinazoline (reference example 21.8) and N-(2-methoxyethyl)-N-methylamine in 60% yield; Mass Spectrum MH⁺ 609.

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Example 19.2**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(2-(1-methylpiperazin-4-yl)ethoxy)-5-cyclopentyloxyquinazoline hydrochloride**

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-7-(2-chloroethoxy)-5-cyclopentyloxyquinazoline (reference example 21.9) and 1-methylpiperazine in 62% yield; Mass Spectrum MH^+ 606.

Example 19.3**4-(3-Chloro-4-fluoroanilino)-7-(3-(pyrrolidin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting pyrrolidine and 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) in 64% yield; NMR Spectrum (DMSO- d_6) 1.67 (m, 4H), 1.92 (m, 2H), 2.15 (m, 1H), 2.30 (m, 1H), 2.45 (m, 4H), 2.55 (t, 2H), 3.78 - 3.98 (m, 3H), 4.15 - 4.20 (m, 3H), 5.45 (m, 1H), 6.80 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.47 (s, 1H), 9.87 (s, 1H); Mass spectrum MH^+ 488.

Example 19.4**4-(3-Chloro-4-fluoroanilino)-7-(3-piperidinopropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and piperidine in 64% yield; NMR spectrum (DMSO- d_6) 1.38 (m, 2H), 1.48 (m, 4H), 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.40 (m, 7H), 3.78 - 3.98 (m, 3H), 4.10 - 4.20 (m, 3H), 5.45 (m, 1H), 6.79 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.85 (s, 1H); Mass spectrum MH^+ 502.

Example 19.5**4-(3-Chloro-4-fluoroanilino)-7-(3-morpholinopropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and morpholine in 64% yield; NMR spectrum (DMSO- d_6) 1.92 (m, 2H), 2.18 (m, 1H), 2.22 - 2.45 (m, 7H), 3.58 (m, 4H), 3.78 - 3.98 (m, 3H), 4.10 - 4.20 (m, 3H), 5.48 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.83 (s, 1H); Mass spectrum MH^+ 504.

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Example 19.6**4-(3-Chloro-4-fluoroanilino)-7-(3-(N-methyl-N-(2-propynyl)amino)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and N-methyl-N-propargylamine in 53% yield; NMR spectrum (DMSO-d₆) 1.88 (m, 2H), 2.18 (m, 1H), 2.20 (s, 3H), 2.22 - 2.40 (m, 1H), 2.50 (m, 2H), 3.08 (t, 1H), 3.28 (m, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.20 (m, 3H), 5.48 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.83 (s, 1H); Mass spectrum MH⁺ 486.

10 Example 19.7**4-(3-Chloro-4-fluoroanilino)-7-(3-(N-methyl-N-allylamino)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and N-methyl-N-allylamine in 37% yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.10 - 2.20 (m, 4H), 2.22 - 2.40 (m, 1H), 2.45 (m, 2H), 2.98 (d, 2H), 3.78-3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.05 - 5.20 (m, 2H), 5.48 (m, 1H), 5.80 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.83 (s, 1H); Mass spectrum MH⁺ 488.

Example 19.8**20 4-(3-Chloro-4-fluoroanilino)-7-(3-(4-hydroxypiperidin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and 4-hydroxypiperidine in 78% yield; NMR spectrum (DMSO-d₆) 1.38 (m, 2H), 1.70 (m, 2H), 1.90 (m, 2H), 2.01 (m, 2H), 2.18 (m, 2H), 2.32 (m, 1H), 2.40 (m, 2H), 2.70 (m, 2H), 3.42 (m, 1H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 4.50 (m, 1H), 5.48 (m, 1H), 6.80 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH⁺ 518.

Example 19.9**30 4-(3-Chloro-4-fluoroanilino)-7-(3-(3-oxo-piperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and piperazin-2-one in 76%

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yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.32 (m, 1H), 2.45 - 2.60 (m, 4H), 2.95 (s, 2H), 3.15 (m, 2H), 3.78 - 3.98 (m, 3H), 4.13 - 4.21 (m, 3H), 5.48 (m, 1H), 6.80 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 7.70 (s, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH⁺ 517.

5 Example 19.10

4-(3-Chloro-4-fluoroanilino)-7-(3-(4-methylpiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and 1-methylpiperazine in 41% yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.10 - 2.20 (m, 4H), 2.21 - 2.42 (m, 11H), 3.78 - 3.98 (m, 3H), 4.13 - 4.21 (m, 3H), 5.48 (m, 1H), 6.80 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH⁺ 517.

Example 19.11

4-(3-Chloro-4-fluoroanilino)-7-(3-(4-(2-methoxyethyl)piperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and 4-(2-methoxyethyl)piperazine in 49% yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.45 (m, 13H), 3.20 (s, 3H), 3.40 (t, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.48 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH⁺ 561.

Example 19.12

4-(3-Chloro-4-fluoroanilino)-7-(3-(4-(N,N-dimethylcarbamoylmethyl)piperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and 1-(N,N-dimethylcarbamoylmethyl)piperazine in 62% yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 11H), 2.78 (s, 3H), 2.99 (s, 3H), 3.27 (s, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.48 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH⁺ 588.

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Example 19.13**4-(3-Chloro-4-fluoroanilino)-7-(3-(4-allylpiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and 1-allylpiperazine in 50% yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 11H), 2.90 (d, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.10 (m, 2H), 5.45 (m, 1H), 5.78 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH⁺ 543.

10 Example 19.14**4-(3-Chloro-4-fluoroanilino)-7-(3-(4-(2-propynyl)piperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and 1-(2-propynyl)piperazine in 53% yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 11H), 3.08 (t, 1H), 3.22 (d, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.47 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH⁺ 541.

Example 19.15**20 4-(3-Chloro-4-fluoroanilino)-7-(3-(4-cyanomethylpiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and 1-cyanomethylpiperazine in 40% yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 11H), 3.68 (s, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.47 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH⁺ 542.

Example 19.16**4-(3-Chloro-4-fluoroanilino)-7-(3-(piperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

30 Obtained by reacting 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21) and piperazine in 71% yield; NMR spectrum (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 7H), 2.70 (m, 4H),

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3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.47 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH^+ 503.

Example 19.17

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline

Obtained by reacting 1-methylpiperazine and 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-chloropropyl-1-yloxy)quinazoline (reference example 21.10) in 41% yield; NMR spectrum ($CDCl_3$) 2.0 (m, 4H), 2.2 - 2.4 (m, 10H), 2.4 - 2.6 (m, 10H), 2.8 (m, 2H), 4.1 (t, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH^+ 649.

Example 19.18

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-piperidinopropoxy)quinazoline

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-chloropropyl-1-yloxy)quinazoline (reference example 21.10) with piperidine in 44% yield; NMR spectrum ($CDCl_3$) 1.5 (m, 2H), 1.6 (m, 4H), 2.0 (m, 4H), 2.2 - 2.4 (m, 11H), 2.5 (m, 2H), 2.8 (m, 2H), 4.1 (t, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH^+ 634.

Example 19.19

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-morpholinopropoxy)quinazoline

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-chloropropyl-1-yloxy)quinazoline (reference example 21.10) with morpholine in 39% yield; NMR spectrum ($CDCl_3$) 2.0 - 2.2 (m, 4H), 2.3 (m, 2H), 2.4 (s, 3H), 2.5 - 2.6 (m, 7H), 2.8 (m, 2H), 3.6 (d, 1H), 3.8 (m, 4H), 4.2 (t, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.4 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH^+ 636.

Example 19.20

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-(N-(2-methoxyethyl)-N-methylamino)propoxy)quinazoline

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Obtained by reacting 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-chloropropyl-1-yloxy)quinazoline (reference example 21.10) with N-(2-methoxyethyl)-N-methylamine in 35% yield; NMR spectrum (CDCl₃) 2.0 (m, 4H), 2.2 - 2.4 (m, 10H), 2.6 (m, 4H), 2.8 (m, 2H), 3.3 (s, 3H), 3.5 (t, 2H), 4.1 (t, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 638.

Example 19.21**4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(2-(4,4-difluoropiperidin-1-yl)ethoxy)quinazoline**

10 Obtained by reacting 4,4-difluoropiperidine and 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(2-chloroethoxy)quinazoline (reference example 21.11) in 23% yield; NMR spectrum (CDCl₃) 1.9 - 2.1 (m, 6H), 2.3 (m, 2H), 2.8 (t, 4H), 3.0 (t, 2H), 3.6 (m, 2H), 4.1 (dt, 2H), 4.3 (t, 2H), 4.8 (m, 1H) 5.2 (s, 2H), 6.6 (d, 1H), 7.0 (d, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.8 (d, 1H), 8.6 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 643.

Example 19.22**4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(3-(N-(2-methoxyethyl)-N-methylamino)propoxy)quinazoline**

20 Obtained by reacting 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(3-chloropropyl-1-yloxy)quinazoline (reference example 21.12) with N-(2-methoxyethyl)-N-methylamine in 52% yield; NMR spectrum (DMSO-d₆) 1.8 - 2.0 (m, 2H), 2.0 - 2.2 (m, 4H), 2.7 (m, 3H), 3.1 (m, 4H), 3.3 (s, 3H), 3.6 (m, 2H), 3.7 (m, 2H), 3.9 (m, 2H), 4.2 (m, 2H), 5.0 (m, 1H), 5.3 (s, 2H), 6.9 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 625.

Example 19.23**4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(3-piperidinopropoxy)quinazoline**

30 Obtained by reacting 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(3-chloropropyl-1-yloxy)quinazoline (reference example 21.12) with piperidine in 39% yield; NMR spectrum (DMSO-d₆) 1.6 (m, 2H), 1.8 - 2.0 (m, 6H), 2.2 (m, 4H), 3.2 (m, 6H), 3.6 (t, 2H), 4.0 (m, 2H), 4.3 (m, 2H), 5.0 (m, 1H), 5.3 (s, 2H), 6.9 (s, 2H), 7.2 - 7.4 (m, 4H), 7.5 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 621.

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Example 19.24**4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(2-chloroethoxy)quinazoline (reference example 21.11) with 1-methylpiperazine in 43% yield; NMR spectrum (CDCl₃) 1.9 (m, 2H), 2.2 - 2.3 (m, 5H), 2.5 (m, 4H), 2.6 (m, 4H), 2.9 (t, 2H), 3.6 (m, 2H), 4.1 (dt, 2H), 4.2 (t, 2H), 4.7 (m, 1H) 5.1 (s, 2H), 6.6 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 622.

10 Example 19.25**4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(3-(4-methylpiperazin-1-yl)propoxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-(3-chloropropyl-1-yloxy)quinazoline (reference example 21.12) with 1-methylpiperazine in 59% yield; NMR spectrum (CDCl₃) 2.0 (m, 4H), 2.3 (m, 5H), 2.4 - 2.6 (m, 10H), 3.6 (m, 2H), 4.1 (dt, 2H), 4.1 (t, 2H), 4.8 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH⁺ 636.

Example 19.26**20 4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-7-(3-(4-methylpiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 1-methylpiperazine with 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21.13) in 43% yield; NMR spectrum (DMSO-d₆) 2.0 (m, 2H), 2.2 (m, 5H), 2.3 - 2.5 (m, 10H), 3.8 - 4.0 (m, 3H), 4.2 (m, 3H), 5.3 (s, 2H) 5.5 (m, 1H), 6.8 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 - 7.6 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 622.

Example 19.27**30 4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-7-(3-piperidinopropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21.13) with

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10 piperidine in 23% yield; NMR spectrum (DMSO-d₆) 1.4 (m, 2H), 1.5 - 1.6 (m, 4H), 1.9 - 2.0 (m, 2H), 2.2 - 2.3 (m, 1H), 2.3 - 2.5 (m, 7H), 3.8 - 4.0 (m, 3H), 4.2 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.1-7.4 (m, 4H), 7.5 (m, 1H), 7.6 (dd, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 607.

15 Example 19.28

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydrofuran-3-yloxy)-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazoline

Obtained by reacting 1-methylpiperazine with 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-7-(2-chloroethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline
10 (reference example 21.14) in 53% yield; NMR spectrum (DMSO-d₆) 2.2 - 2.3 (m, 4H), 2.3 - 2.4 (m, 5H), 2.5 (m, 2H - hidden under DMSO signal), 2.8 (m, 2H), 3.4 (m, 2H - partially obscured by water signal), 3.8 - 4.0 (m, 3H), 4.2 - 4.3 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.9 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5-7.6 (m, 2H), 8.2 (m, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 622.

15 Example 19.29

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-morpholinopropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21.13) with
20 morpholine in 14% yield; NMR spectrum (DMSO-d₆) 2.0 (m, 2H), 2.2 (m, 1H), 2.3 - 2.5 (m, 7H), 3.6 (m, 4H), 3.8 - 4.0 (m, 3H), 4.2 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 - 7.6 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Mass spectrum MH⁺ 609.

Example 19.30

25 4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(2-morpholinoethoxy)-5-(tetrahydrofuran-3-yloxy)-quinazoline

Obtained by reacting 7-(2-chloroethoxy)-4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21.14) with morpholine in 33%
yield; NMR spectrum (DMSO-d₆) 2.2 (m, 1H), 2.4 (m, 1H), 2.5 (m, 2H - hidden under DMSO signal), 2.8 (t, 2H), 3.3 (m, 2H - partially obscured by water signal), 3.6 (m, 4H), 3.8 -
30 4.0 (m, 3H), 4.2 (d, 1H), 4.3 (t, 2H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.2-7.4 (m, 4H), 7.5 (m, 1H), 7.6 (dd, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 595.

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Example 19.31**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(2-[N-(2-methoxyethyl)-N-methylamino]ethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 7-(2-chloroethoxy)-4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21.14) with N-(2-methoxyethyl)-N-methylamine in 25% yield; NMR spectrum (DMSO-d₆) 2.2 (m, 1H), 2.3 (s, 3H), 2.7 (t, 2H), 2.9 (t, 2H), 3.3 (s, 3H), 3.3 (m, 1H), 3.5 (t, 2H), 3.8 - 4.0 (m, 3H), 4.2 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 - 7.6 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 597.

10 Example 19.32**4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(2-piperidinoethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Obtained by reacting 7-(2-chloroethoxy)-4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 21.14) with piperidine in 34% yield; NMR spectrum (DMSO-d₆) 1.4 (m, 2H), 1.5 - 1.6 (m, 4H), 2.2 - 2.3 (m, 1H), 2.3 - 2.4 (m, 1H), 2.5 (m, 2H), 2.8 (m, 2H), 3.2 (m, 2H), 3.9 - 4.0 (m, 3H), 4.2 - 4.3 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 (m, 1H), 7.6 (dd, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 593.

Example 20**20 4-(3-Chloro-4-fluoroanilino)-7-(3-(4-acetyl piperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline**

Triethylamine (38 µl) and acetic anhydride (26 µl) were added, each in one portion, to a stirred solution of 4-(3-chloro-4-fluoroanilino)-7-(3-(piperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline (example 19.16) (115 mg) in DCM (2 ml) at 0°C. The solution was stirred at 0°C under a nitrogen atmosphere for 1 hour and then DCM (10 ml) and saturated aqueous sodium hydrogen carbonate (15 ml) were added. The layers were separated and the aqueous layer was extracted with DCM (2 × 10 ml). The combined organic extracts were dried and concentrated *in vacuo* to leave a white solid which was purified by chromatography using 0 - 8% 7N ammonia in methanol in DCM as eluent. This gave the title compound as a white solid (105 mg, 84%); NMR Spectrum (DMSO-d₆) 1.90 - 2.00 (m, 5H), 2.18 (m, 1H), 2.22 - 2.50 (m, 7H), 3.42 (m, 4H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H),

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5.47 (m, 1H), 6.80 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Mass spectrum MH^+ 545.

Example 21

4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(1-

5 methylpiperidin-4-ylmethoxy)quinazoline

4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-(piperidin-4-ylmethoxy)quinazoline (130 mg) (example 13.2) was added to a mixture of formic acid (0.58 ml) and formaldehyde (37 wt. % aqueous solution, 0.88 ml), and the resultant mixture was heated at 85°C for 2 hours. An excess of saturated aqueous sodium hydrogen carbonate solution was added, and the product was extracted into DCM. The combined organic extracts were dried and concentrated *in vacuo* to give the crude product, which was triturated under cold methanol to give the title compound as a white solid (20 mg, 15%); NMR spectrum ($CDCl_3$) 1.5 (m, 2H), 1.8 (m, 3H), 2.0 (m, 4H), 2.2 - 2.4 (m, 10H), 2.8 (m, 2H), 2.9 (m, 2H), 3.9 (d, 2H), 4.6 (m, 1H) 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 15 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH^+ 620.

Example 22

4-(1-(2-Cyanobenzyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

20 Sodium hydride (13.1 mg) was added to a solution of 4-(indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.8) (120 mg) in DMA (1 ml), and stirred at room temperature for 30 minutes. This mixture was then added dropwise to a solution of 2-chloromethylbenzonitrile (50 mg) in DMA (1 ml), and allowed to stir for 5 hours at room temperature. Excess water was added, which gave the product as a thick gum, 25 which was decanted off. The gum was then purified by chromatography, using 0-10% methanol in DCM as eluent to give the product as a gum, which was triturated under water, to give the title compound as a solid (10 mg, 6%); Mass Spectrum MH^+ 519.

The procedure described above was repeated using the appropriate alkyl halide. Thus were obtained the compounds described below:

30 Example 22.1

4-(1-(3-Fluorobenzyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

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Obtained by reacting 4-(indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.8) with 3-fluorobenzyl chloride in 14% yield; Mass Spectrum MH^+ 512.

Example 22.2

5 4-(1-(2-Fluorobenzyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-(indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.8) with 2-fluorobenzyl chloride in 5% yield; Mass Spectrum MH^+ 512.

10 Example 22.3

4-(1-(5-methylisoxazol-3-ylmethyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-(indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.8) with 3-(chloromethyl)-5-methylisoxazole in 74% yield;

15 Mass Spectrum MH^+ 499.

Example 22.4

4-(1-Benzylindol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 4-(indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.8) with benzyl chloride in 46% yield; Mass Spectrum MH^+

20 494.

Example 22.5

7-Methoxy-5-(1-methylpiperidin-4-yloxy)-4-(1-(2-pyridylmethyl)indol-5-ylamino)quinazoline

Obtained by reacting 4-(indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.8) with 2-picolyl chloride in 35% yield; Mass Spectrum MH^+

25 Example 22.6

7-Methoxy-5-(1-methylpiperidin-4-yloxy)-4-(1-(thiazol-4-ylmethyl)indol-5-ylamino)quinazoline

Obtained by reacting 4-(indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.8) with 4-(chloromethyl)thiazole in 57% yield; Mass Spectrum MH^+ 501.

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Example 22.7**4-(1-(2,6-Difluorobenzyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained by reacting 4-(indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline (example 2.8) with 2,6-difluorobenzyl chloride in 43% yield; **Mass Spectrum** MH⁺ 530.

Example 23

The compounds shown in bold in Table 1 were prepared as follows:

- Amines (1.2 mM) were dissolved in NMP (1 ml) and 50 µl of each solution transferred to a 96 well plate. Stock solutions of the 4 substrates;
- Substrate A** 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 21.2) (120mg);
- Substrate B** 7-(2-chloroethoxy)-4-(3-chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 21.6) (116mg);
- Substrate C** 4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydropyran-4-yloxy)quinazoline (reference example 21.3) (117mg) and
- Substrate D** 7-(2-chloroethoxy)-4-(3-chloro-4-fluoroanilino)-5-(tetrahydropyran-4-yloxy)quinazoline (reference example 21.7) (113 mg) in NMP (1.25 ml) were prepared, and 50 µl aliquots added to each well containing the amine solution shown in Table 1. The plate was heated and agitated at 80°C for 60 hours, allowed to cool, then concentrated *in vacuo*. To each well was added DMSO (550 µl). Aliquots of 50 µl were then taken from each well for LCMS purity determination. LCMS purity was determined on a Phenomenex Synergi column (reverse phase silica, 50 x 2 mm, flow rate 1.1 ml/minute), eluting with acetonitrile-water containing formic acid (0.05%) on a gradient from 5-95% over 4.5 minutes, with UV detection at 254 nm. There was thus obtained the compound shown in bold in Table 1.

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Table 1

In table 1, EG refers to Example, RT refers to the LCMS retention time (minutes)

EG	Compound	M-H ⁺	RT
23.1	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-hydroxyethyl)-N-methylamino)propoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate A with N-(2-hydroxyethyl)-N-methylamine	517	0.84
23.2	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(3-hydroxypyrrolidin-1-yl)propoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate A with 3-hydroxypyrrolidine	528	0.86
23.3	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(4-methylpiperazin-1-yl)propoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate A with 1-methylpiperazine	542	0.93
23.4	<u>4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-piperidinopropoxy)quinazoline</u> Obtained by reacting Substrate A with piperidine	527	0.96
23.5	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(N-methyl-N-(1-methylpyrrolidin-3-yl)amino)propoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate A with N-(1-methylpyrrolidin-3-yl)-N-methylamine	556	0.88
23.6	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(2-methoxyethyl)piperazin-1-yl)propoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate A with 1-(2-methoxyethyl)piperazine.	586	0.98
23.7	<u>4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-pyrrolidin-1-ylpropoxy)quinazoline</u> Obtained by reacting Substrate A with pyrrolidine	513	0.90
23.8	<u>4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-morpholinopropoxy)quinazoline</u> Obtained by reacting Substrate A with morpholine	529	1.06
23.9	<u>4-(3-Chloro-4-fluoroanilino)-7-(3-homopiperidin-1-ylpropoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate A with homopiperidine	542 (MH ⁺)	1.00
23.10	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-dimethylaminoethyl)-N-methylamino)propoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate A with N,N,N'-trimethylethylene diamine	544	0.97

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EG	Compound	M-H ⁺	RT
23.11	4-(3-Chloro-4-fluoroanilino)-7-(3-(4-methylhomopiperazin-1-yl)propoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline Obtained by reacting Substrate A with 1-methylhomopiperazine	555 (MH ⁺)	0.92
23.12	4-(3-Chloro-4-fluoroanilino)-7-[2-(N-(2-hydroxyethyl)-N-methylamino)ethoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline Obtained by reacting Substrate B with N-(2-hydroxyethyl)-N-methylamine	503	0.77
23.13	~~4-(3-Chloro-4-fluoroanilino)-7-(2-(3-hydroxypyrrolidin-1-yl)ethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline~~ Obtained by reacting Substrate B with 3-hydroxypyrrolidine	515	0.76
23.14	4-(3-Chloro-4-fluoroanilino)-7-(2-(4-methylpiperazin-1-yl)ethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline Obtained by reacting Substrate B with 1-methylpiperazine	528	0.84
23.15	4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(2-piperidinoethoxy)quinazoline Obtained by reacting Substrate B with piperidine	514 (MH ⁺)	1.01
23.16	4-(3-Chloro-4-fluoroanilino)-7-[2-(N-methyl-N-(1-methylpyrrolidin-3-yl)amino)ethoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline Obtained by reacting Substrate B with N-(1-methylpyrrolidin-3-yl)-N-methylamine	544 (MH ⁺)	0.90
23.17	4-(3-Chloro-4-fluoroanilino)-7-(2-(4-(2-methoxyethyl)piperazin-1-yl)ethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline Obtained by reacting Substrate B with 1-(2-methoxyethyl)piperazine	574 (MH ⁺)	1.06
23.18	4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(2-pyrrolidin-1-ylethoxy)quinazoline Obtained by reacting Substrate B with pyrrolidine	499	0.89
23.19	4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(2-morpholinoethoxy)quinazoline Obtained by reacting Substrate B with morpholine	515	1.22
23.20	4-(3-Chloro-4-fluoroanilino)-7-(2-homopiperidin-1-ylethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline Obtained by reacting Substrate B with homopiperidine	527	1.03

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EG	Compound	M-H ⁺	RT
23.21	<u>4-(3-Chloro-4-fluoroanilino)-7-[2-(N-(2-dimethylaminoethyl)-N-methylamino)ethoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate B with N,N,N'-trimethylethylene diamine	530	0.93
23.22	<u>4-(3-Chloro-4-fluoroanilino)-7-[2-(4-methylhomopiperazin-1-yl)ethoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate B with 1-methylhomopiperazine	544 (MH ⁺)	0.96
23.23	<u>4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(2-(4-isopropylpiperazin-1-yl)ethoxy)quinazoline</u> Obtained by reacting Substrate B with 1-isopropylpiperazine	556	0.99
23.24	<u>4-(3-Chloro-4-fluoroanilino)-7-[2-(N-(2-methoxyethyl)-N-methylamino)ethoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate B with N-(2-methoxyethyl)-N-methylamine	517	0.95
23.25	<u>4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(2-(4-(2-morpholinoethyl)piperazin-1-yl)ethoxy)quinazoline</u> Obtained by reacting Substrate B with 1-(2-morpholinoethyl)piperazine	627	1.04
23.26	<u>4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-[2-(4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl)ethoxy]quinazoline</u> Obtained by reacting Substrate B with 1-(tetrahydrofuran-2-ylmethyl)piperazine	598	1.10
23.27	<u>4-(3-Chloro-4-fluoroanilino)-7-[2-(3-dimethylaminopyrrolidin-1-yl)ethoxy]-5-(1-methylpiperidin-4-yloxy)quinazoline</u> Obtained by reacting Substrate B with 3-dimethylaminopyrrolidine	542	0.98
23.28	<u>4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-[2-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)ethoxy]quinazoline</u> Obtained by reacting Substrate B with 1-(1-methylpiperidin-4-yl)piperazine	611	1.08
23.29	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-hydroxyethyl)-N-methylamino)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with N-(2-hydroxyethyl)-N-	505 (MH ⁺)	1.56

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EG	Compound	M-H ⁺	RT
	methylamine		
23.30	<u>4-(3-Chloro-4-fluoroanilino)-7-(3-(3-hydroxypyrrolidin-1-yl)propoxy)-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with 3-hydroxypyrrolidine	516	1.54
23.31	<u>4-(3-Chloro-4-fluoroanilino)-7-(3-(4-methylpiperazin-1-yl)propoxy)-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with 1-methylpiperazine	531 (MH ⁺)	1.64
23.32	<u>4-(3-Chloro-4-fluoroanilino)-7-(3-piperidinopropoxy)-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with piperidine	514	1.64
23.33	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(2-methoxyethyl)piperazin-1-yl)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with 1-(2-methoxyethyl)piperazine	574 (MH ⁺)	1.68
23.34	<u>4-(3-Chloro-4-fluoroanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with pyrrolidine	500	1.59
23.35	<u>4-(3-Chloro-4-fluoroanilino)-7-(3-morpholinopropoxy)-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with morpholine	516	1.85
23.36	<u>4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-dimethylaminoethyl)-N-methylamino)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with 1, 1, 2-trimethylethylene diamine	531	1.67
23.37	<u>4-(3-Chloro-4-fluoroanilino)-7-(3-(4-methylhomopiperazin-1-yl)propoxy)-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with 1-methylhomopiperazine	543	1.55
23.38	<u>4-(3-Chloro-4-fluoroanilino)-7-(3-(4-isopropylpiperazin-1-yl)propoxy)-5-(tetrahydropyran-4-yloxy)quinazoline</u> Obtained by reacting Substrate C with 1-isopropylpiperazine	557	1.66

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RG	Compound	M-H ⁺	RT
23.39	4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-methoxyethyl)-N-methylamino)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate C with N-(2-methoxyethyl)-N-methylamine	518	1.64
23.40	4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(2-morpholinoethyl)piperazin-1-yl)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate C with 1-(2-morpholinoethyl)piperazine	628	1.40
23.41	~~4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline~~ Obtained by reacting Substrate C with 1-(tetrahydrofuran-2-yl-methyl)piperazine	601 (MH ⁺)	1.76
23.42	~~4-(3-Chloro-4-fluoroanilino)-7-[3-(3-dimethylaminopyrrolidin-1-yl)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline~~ Obtained by reacting Substrate C with 3-dimethylaminopyrrolidine	545 (MH ⁺)	1.61
23.43	4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)propoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate C with 1-(1-methylpiperidin-4-yl)piperazine	612	1.27
23.44	~~4-(3-Chloro-4-fluoroanilino)-7-[2-(N-(2-hydroxyethyl)-N-methylamino)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline~~ Obtained by reacting Substrate D with N-(2-hydroxyethyl)-N-methylamine	490	1.53
23.45	~~4-(3-Chloro-4-fluoroanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline~~ Obtained by reacting Substrate D with 1-methylpiperazine	515	1.59

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EG	Compound	M-H ⁺	RT
23.46	4-(3-Chloro-4-fluoroanilino)-7-(2-piperidinoethoxy)-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with piperidine	500	1.64
23.47	4-(3-Chloro-4-fluoroanilino)-7-[2-(N-methyl-N-(1-methylpyrrolidin-3-yl)amino)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with N-(1-methylpyrrolidin-3-yl)-N-methylamine	529	1.54
23.48	4-(3-Chloro-4-fluoroanilino)-7-(2-(4-(2-methoxyethyl)piperazin-1-yl)ethoxy)-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with 1-(2-methoxyethyl)piperazine	559	1.66
23.49	~~4-(3-Chloro-4-fluoroanilino)-7-(2-(homopiperidin-1-yl)ethoxy)-5-(tetrahydropyran-4-yloxy)quinazoline~~ Obtained by reacting Substrate D with homopiperidine	514	1.69
23.50	4-(3-Chloro-4-fluoroanilino)-7-[2-(N-(2-dimethylaminoethyl)-N-methylamino)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with N,N,N'-trimethylethylene diamine	517	1.60
23.51	4-(3-Chloro-4-fluoroanilino)-7-(2-(4-methylhomopiperazin-1-yl)ethoxy)-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with 1-methylhomopiperazine	529	1.60
23.52	4-(3-Chloro-4-fluoroanilino)-7-(2-(4-isopropylpiperazin-1-yl)ethoxy)-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with 1-isopropylpiperazine	543	1.61
23.53	4-(3-Chloro-4-fluoroanilino)-7-[2-(N-methyl-N-(2-methoxyethyl)amino)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with N-(2-methoxyethyl)-N-methylamine	504	1.65

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EG	Compound	M-H ⁺	RT
23.54	4-(3-Chloro-4-fluoroanilino)-7-[2-(4-(2-morpholinoethyl)piperazin-1-yl)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with 1-(2-morpholinoethyl)piperazine	616 (MH ⁺)	1.48
23.55	4-(3-Chloro-4-fluoroanilino)-7-[2-(4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with 1-(tetrahydrofuran-2-ylmethyl)piperazine	587 (MH ⁺)	1.71
23.56	4-(3-Chloro-4-fluoroanilino)-7-[2-(3-dimethylaminopyrrolidin-1-yl)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with 3-dimethylaminopyrrolidine	529	1.59
23.57	4-(3-Chloro-4-fluoroanilino)-7-[2-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)ethoxy]-5-(tetrahydropyran-4-yloxy)quinazoline Obtained by reacting Substrate D with 1-(1-methylpiperidin-4-yl)piperazine	598	1.35

Example 24

The compounds shown in bold in Table 2 were prepared as follows:

Amines (1.2 mM) were dissolved in NMP (1 ml) and 50 µl of each solution transferred to a

5 96 well plate. Stock solutions of the 4 substrates;

Substrate E **4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline** (reference example 21) (113mg);

Substrate F **7-(2-chloroethoxy)-4-(3-chloro-4-fluoroanilino)-5-(tetrahydrofuran-3-yloxy)quinazoline** (reference example 21.4) (110 mg);

10 Substrate G **4-(3-chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-cyclopentyloxyquinazoline** (reference example 21.1) (113mg) and

Substrate H **7-(2-chloroethoxy)-4-(3-chloro-4-fluoroanilino)-5-cyclopentyloxyquinazoline** (reference example 21.5) (109mg) in NMP (1.25 ml) were prepared, and 50 µl aliquots added to each well containing the amine solution shown in Table 2. The plate was heated and

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agitated at 80°C for 60 hours, allowed to cool, then concentrated *in vacuo*. To each well was added DMSO (550 µl). Aliquots of 50 µl were then taken from each well for LCMS purity determination. LCMS purity was determined on a Phenomenex Synergi column (reverse phase silica, 50 x 2 mm, flow rate 1.1 ml/minute), eluting with acetonitrile-water containing 5 formic acid (0.05%) on a gradient from 5-95% over 4.5 minutes, with UV detection at 254 nm. There was thus obtained the compounds shown in bold in Table 2.

Table 2

In Table 2 EG refers to Example, RT refers to the LCMS retention time (minutes)

EG	Compound	M-H⁺	RT
24.1	4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-hydroxyethyl)-N-methylamino)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with N-(2-hydroxyethyl)-N-methylamine	490	1.09
24.2	4-(3-Chloro-4-fluoroanilino)-7-(3-(3-hydroxypyrrolidin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 3-hydroxypyrrolidine	502	1.14
24.3	4-(3-Chloro-4-fluoroanilino)-7-(3-(4-methylpiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 1-methylpiperazine	515	1.08
24.4	4-(3-Chloro-4-fluoroanilino)-7-(3-piperidinopropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with piperidine	500	1.20
24.5	4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(2-methoxyethyl)piperazin-1-yl)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 1-(2-methoxyethyl)piperazine	559	1.13
24.6	4-(3-Chloro-4-fluoroanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with pyrrolidine	486	1.19
24.7	4-(3-Chloro-4-fluoroanilino)-7-(3-morpholinopropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with morpholine	502	1.14

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EG	Compound	M-H ⁺	RT
24.8	4-(3-Chloro-4-fluoroanilino)-7-(3-homopiperidin-1-ylpropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with homopiperidine	514	1.26
24.9	4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-dimethylaminoethyl)-N-methylamino)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with N,N,N'-trimethylethylene diamine	517	0.94
24.10	4-(3-Chloro-4-fluoroanilino)-7-(3-(4-methylhomopiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 1-methylhomopiperazine	529	0.91
24.11	4-(3-Chloro-4-fluoroanilino)-7-(3-(4-isopropylpiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 1-isopropylpiperazine	543	1.12
24.12	4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-methoxyethyl)-N-methylamino)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with N-(2-methoxyethyl)-N-methylamine	504	1.19
24.13	4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(2-morpholinoethyl)piperazin-1-yl)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 1-(2-morpholinoethyl)piperazine	614	0.93
24.14	4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 1-(tetrahydrofuran-2-ylmethyl)piperazine	585	1.18
24.15	4-(3-Chloro-4-fluoroanilino)-7-[3-(3-dimethylaminopyrrolidin-1-yl)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 3-dimethylaminopyrrolidine	529	0.94

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EG	Compound	M-H ⁺	RT
24.16	4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate E with 1-(1-methylpiperidin-4-yl)piperazine	598	0.92
24.17	4-(3-Chloro-4-fluoroanilino)-7-[2-(N-(2-hydroxyethyl)-N-methylamino)ethoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with N-(2-hydroxyethyl)-N-methylamine	477 (MH ⁺)	1.12
24.18	4-(3-Chloro-4-fluoroanilino)-7-[2-(3-hydroxypyrrolidin-1-yl)ethoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with 3-hydroxypyrrolidine	488	1.12
24.19	4-(3-Chloro-4-fluoroanilino)-7-(2-(4-methylpiperazin-1-yl)ethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with 1-methylpiperazine	501	1.09
24.20	4-(3-Chloro-4-fluoroanilino)-7-(2-piperidinoethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with piperidine	486	1.19
24.21	4-(3-Chloro-4-fluoroanilino)-7-[2-(4-(2-methoxyethyl)piperazin-1-yl)ethoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with 1-(2-methoxyethyl)piperazine	545	1.15
24.22	<u>4-(3-Chloro-4-fluoroanilino)-7-(2-pyrrolidin-1-ylethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline</u> Obtained by reacting Substrate F with pyrrolidine	472	1.15
24.23	4-(3-Chloro-4-fluoroanilino)-7-(2-morpholinoethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with morpholine	488	1.15



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<u>EG</u>	<u>Compound</u>	<u>M-H⁺</u>	<u>RT</u>
24.24	4-(3-Chloro-4-fluoroanilino)-7-(2-homopiperidin-1-yloxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with homopiperidine	499	1.28
24.25	4-(3-Chloro-4-fluoroanilino)-7-(2-(4-methylhomopiperazin-1-yl)ethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with 1-methylhomopiperazine	515	0.98
24.26	4-(3-Chloro-4-fluoroanilino)-7-(2-(4-isopropylpiperazin-1-yl)ethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline Obtained by reacting Substrate F with 1-isopropylpiperazine	529	1.15
24.27	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline Obtained by reacting Substrate G with pyrrolidine	484	1.45
24.28	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-(3-morpholinopropoxy)quinazoline Obtained by reacting Substrate G with morpholine	500	1.42
24.29	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-(3-homopiperidin-1-ylpropoxy)quinazoline Obtained by reacting Substrate G with homopiperidine	512	1.54
24.30	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-(3-(4-methylhomopiperazin-1-yl)propoxy)quinazoline Obtained by reacting Substrate G with 1-methylhomopiperazine	527	1.17
24.31	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[3-(4-isopropylpiperazin-1-yl)propoxy]quinazoline Obtained by reacting Substrate G with 1-isopropylpiperazine	541	1.39
24.32	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[3-(N-(2-methoxyethyl)-N-methylamino)propoxy]quinazoline Obtained by reacting Substrate G with N-(2-methoxyethyl)-N-methylamine	502	1.47

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<u>EG</u>	<u>Compound</u>	<u>M-H⁺</u>	<u>RT</u>
24.33	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[3-(4-(2-morpholinoethyl)piperazin-1-yl)propoxy]quinazoline Obtained by reacting Substrate G with 1-(2-morpholinoethyl)piperazine	612	1.16
24.34	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[3-(4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl)propoxy]quinazoline Obtained by reacting Substrate G with 1-(tetrahydrofuran-2-yl-methyl)piperazine	583	1.45
24.35	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[3-(3-dimethylamino pyrrolidin-1-yl)propoxy]quinazoline Obtained by reacting Substrate G with 3-dimethylaminopyrrolidine	527	1.18
24.36	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[3-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)propoxy]quinazoline Obtained by reacting Substrate G with 1-(1-methylpiperidin-4-yl)piperazine	596	1.16
24.37	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[2-(N-(2-hydroxyethyl)-N-methylamino)ethoxy]quinazoline Obtained by reacting Substrate H with N-(2-hydroxyethyl)-N-methylamine	474	1.35
24.38	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[2-(3-hydroxypyrrolidin-1-yl)ethoxy]quinazoline Obtained by reacting Substrate H with 3-hydroxypyrrolidine	486	1.37
24.39	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-(2-(4-methylpiperazin-1-yl)ethoxy)quinazoline Obtained by reacting Substrate H with 1-methylpiperazine	499	1.37
24.40	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-(2-piperidinoethoxy)quinazoline Obtained by reacting Substrate H with piperidine	484	1.47

<u>EG</u>	<u>Compound</u>	<u>M-H⁺</u>	<u>RT</u>
24.41	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[2-(4-(2-methoxyethyl)piperazin-1-yl)ethoxy]quinazoline Obtained by reacting Substrate H with 1-(2-methoxyethyl)piperazine	543	1.40
24.42	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-(2-homopiperidin-1-ylethoxy)quinazoline Obtained by reacting Substrate H with homopiperidine	498	1.52
24.43	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[2-(4-methylhomopiperazin-1-yl)ethoxy]quinazoline Obtained by reacting Substrate H with 1-methylhomopiperazine	513	1.21
24.44	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[2-(4-(2-morpholinoethyl)piperazin-1-yl)ethoxy]quinazoline Obtained by reacting Substrate H with 1-(2-morpholinoethyl)piperazine	598	1.14
24.45	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[2-(4-(tetrahydrofuran-2-ylmethyl)piperazin-1-yl)ethoxy]quinazoline Obtained by reacting Substrate H with 1-(tetrahydrofuran-2-yl-methyl)piperazine	569	1.45
24.46	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[2-(3-dimethylaminopyrrolidin-1-yl)ethoxy]quinazoline Obtained by reacting Substrate H with 3-dimethylaminopyrrolidine	513	1.20
24.47	4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-[2-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)ethoxy]quinazoline Obtained by reacting Substrate H with 1-(1-methylpiperidin-4-yl)piperazine	582	1.13

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Example 25

Pharmaceutical composition

The following illustrates a representative pharmaceutical dosage form of the invention
5 as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

	(a)	Tablet I	mg/tablet
		Compound X.....	100
10		Lactose Ph.Eur.....	182.75
		Croscarmellose sodium.....	12.0
		Maize starch paste (5% w/v paste).....	2.25
		Magnesium stearate.....	3.0
		:	
15	(b)	Injection I	(50 mg/ml)
		Compound X.....	5.0% w/v
		1M Sodium hydroxide solution.....	15.0% v/v
		0.1M Hydrochloric acid (to adjust pH to 7.6)	
		Polyethylene glycol 400.....	4.5% w/v
20		Water for injection to 100%.	

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. For example the tablet may be prepared by blending the components together and compressing the mixture into a tablet.

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Starting Materials**Reference Example 1****4, 6-Difluoroisatin**

A solution of hydroxylamine hydrochloride (41.7 g) in water (100 ml) was added
5 dropwise to a solution of chloral hydrate (31.6 g) and sodium sulphate (228.3 g) in water (50 ml) at 60°C. The resulting solution was then added to a solution of 3, 5-difluoroaniline (25 g) in water (300 ml) and concentrated HCl (16 ml) at 80°C, and the mixture heated at 95°C for 15 minutes. The resulting white solid was filtered and washed with water. This solid was added in portions to concentrated H₂SO₄ (167 ml) at 60 - 80°C, to give a deep red solution
10 which was stirred for an additional 15 minutes. The solution was poured into ice-water and the resulting orange solid filtered, washed with water, and dried *in vacuo* to yield the title compound (24.64 g, 69%); NMR spectrum (DMSO-d₆) 6.58 (dd, 1H), 6.85 (dt, 1H), 11.36 (bs, 1H); Mass spectrum M-H⁺ 182.

Reference Example 2**15 4,6-Dibenzoyloxyisatin**

3,5-Dibenzoyloxyaniline hydrochloride (reference example 24) (32.33 g) was added cautiously to oxalyl chloride (100 ml) and the solution heated at reflux for 3 hours. The solution was cooled and concentrated *in vacuo*. Methanol (100 ml) was added to the residue and the mixture heated at reflux for 1 hour. The reaction was allowed to cool, and the
20 resulting precipitate filtered and washed with methanol to give the title compound as a yellow solid (16.22 g, 48%); NMR spectrum (DMSO-d₆) 5.22 (s, 2H), 5.24 (s, 2H), 6.10 (s, 1H), 6.38 (s, 1H), 7.30-7.50 (m, 10H), 10.90 (bs, 1H); Mass spectrum M-H⁺ 358.

The procedure described above was repeated using the appropriate aniline hydrochloride. Thus was obtained the compound described below:

25 Reference Example 2.1**4,6-Dimethoxyisatin**

Obtained from 3,5-dimethoxyaniline hydrochloride; NMR spectrum (DMSO-d₆) 3.83 (s, 3H), 3.86 (s, 3H), 6.00 (d, 1H), 6.17 (d, 1H), 10.86 (bs, 1H).

Reference Example 3**30 2-Amino-4,6-difluorobenzoic acid**

4,6-Difluoroisatin (reference example 1) (10 g) was dissolved in 33 % (w/v) aqueous NaOH (85 ml) at 75°C. To this solution was added H₂O₂ (30%, 16 ml) dropwise over 30

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minutes. The reaction was stirred for an hour at 75°C, then cooled to room temperature. Ice was added, and the reaction mixture acidified to pH 1 with concentrated HCl. The resulting precipitate was filtered, washed with water and dried *in vacuo* to give the title compound as a pale yellow solid (6.28 g, 66%) Mass spectrum M^+ 173.

- 5 The procedure described above was repeated using the appropriate isatin. Thus were obtained the compounds described below:

Reference Example 3.1

2-Amino-4,6-dibenzoyloxybenzoic acid

- Obtained from 4,6-dibenzoyloxyisatin (reference example 2) in 87% yield; NMR
10 spectrum (DMSO-d₆) 4.97 (s, 2H), 5.05 (s, 2H), 5.92 (d, 1H), 5.97 (d, 1H), 7.20 - 7.50 (m, 10H).

Reference Example 3.2

2-Amino-4,6-dimethoxybenzoic acid

- Obtained from 4, 6-dimethoxyisatin (reference example 2.1) in 63% yield; NMR
15 spectrum (DMSO-d₆) 3.69 (s, 3H), 3.75 (s, 3H), 5.77 (d, 1H), 5.92 (d, 1H); Mass spectrum MH^+ 198.

Reference Example 4

Methyl 2-amino-4,6-difluorobenzoate

- Dimethyl sulphate (11.76 ml) was added dropwise to a mixture of potassium
20 carbonate (37.8 g) and 2-amino-4,6-difluorobenzoic acid (reference example 3) (21.56 g) in DMF (500 ml) at 0°C. The reaction was stirred for 1 hour, then poured into water. The resulting precipitate was filtered, washed with water and dried *in vacuo* to give the title compound as a beige solid (9.39 g, 40%). The filtrate was extracted with ethyl acetate, and combined organic extracts dried and concentrated *in vacuo* to yield more of the title
25 compound as a yellow crystalline solid (6.57 g, 28%); NMR spectrum (DMSO-d₆) 3.78 (s, 3H), 6.25 (m, 1H), 6.38 (m, 1H), 6.90 (bs, 2H).

The procedure described above was repeated using the appropriate acid. Thus were obtained the compounds described below:

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Reference Example 4.1**Methyl 2-amino-4,6-dibenzyloxybenzoate**

Obtained from 2-amino-4,6-dibenzyloxybenzoic acid (reference example 3.1) in 81% yield; NMR spectrum (DMSO-d₆) 3.72 (s, 3H), 5.02 (s, 2H), 5.07 (s, 2H), 5.96 (s, 1H), 6.03 (s, 1H), 6.20 (bs, 2H), 7.22 - 7.48 (m, 10H); Mass spectrum MH⁺ 364.

Reference Example 4.2**Methyl 2-amino-4,6-dimethoxybenzoate**

Obtained from 2-amino-4,6-dimethoxybenzoic acid (reference example 3.2) in 77% yield; NMR spectrum (DMSO-d₆) 3.66 (s, 3H), 3.67 (s, 3H), 3.68 (s, 3H), 5.75 (d, 1H), 5.90 (d, 1H), 6.13 (s, 2H).

Reference Example 5**5,7-Difluoro-3,4-dihydroquinazolin-4-one**

A solution of methyl 2-amino-4,6-difluorobenzoate (reference example 4) (15.96 g) and formamidine acetate (19.58 g) in 2-methoxyethanol (200 ml) was heated at 120°C for 16 hours. The reaction was cooled, concentrated *in vacuo*, and the residue triturated with methanol to give the title compound as a beige solid (8.09 g, 52%); NMR spectrum (DMSO-d₆) 7.20 - 7.40 (m, 2H), 8.10 (s, 1H), 12.35 (bs, 1H); Mass spectrum M-H⁺ 181.

The procedure described above was repeated using the appropriate anthranilic ester. Thus were obtained the compounds described below:

20 Reference Example 5.1**5,7-Dibenzyloxy-3,4-dihydroquinazolin-4-one**

Obtained from methyl 2-amino-4,6-dibenzyloxybenzoate (reference example 4.1) in 64% yield; NMR spectrum (DMSO-d₆) 5.20 (s, 4H), 6.72 (d, 1H), 6.78 (d, 1H), 7.20 - 7.60 (m, 10H), 7.92 (s, 1H), 11.70 (bs, 1H); Mass spectrum M-H⁺ 357.

25 Reference Example 5.2**3,4-Dihydro-5,7-dimethoxyquinazolin-4-one**

Obtained from methyl 2-amino-4,6-dimethoxybenzoate (reference example 4.2) in 88% yield; NMR spectrum (DMSO-d₆) 3.80 (s, 3H), 3.84 (s, 3H), 6.51 (d, 1H), 6.63 (d, 1H), 7.88 (s, 1H), 11.62 (bs, 1H); Mass spectrum MH⁺ 207.

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Reference Example 6**5-Benzoyloxy-3,4-dihydro-7-fluoroquinazolin-4-one**

Sodium hydride (0.88 g, 60% dispersion in mineral oil) was added portionwise over 5 minutes to benzyl alcohol (1.71 ml) in DMF (30 ml) at 0°C. The reaction was stirred at 0°C for 10 minutes then 5,7-difluoro-3,4-dihydroquinazolin-4-one (reference example 5) (2.00 g) was added in portions over 5 minutes. The resulting solution was allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was concentrated *in vacuo*, water (10 ml) added and then extracted with ethyl acetate (100 ml). A solid precipitated from the organic layer and this was filtered and dried *in vacuo* to afford the title compound as white needles (1.00 g, 34%). The aqueous layer was extracted with ethyl acetate (3 x 100ml), dried, filtered and concentrated *in vacuo* to afford more of the title compound (0.64 g, 22%); NMR spectrum (DMSO-d₆) 5.23 (s, 2H), 6.90 (dd, 1H), 7.00 (dd, 1H), 7.30 (t, 1H), 7.36 (t, 2H), 7.58 (d, 2H), 8.00 (s, 1H), 11.96 (bs, 1H); Mass spectrum MH⁺ 271.

The procedure described above was repeated using the appropriate alcohol. Thus was obtained the compound described below:

Reference Example 6.1**7-Fluoro-5-(tetrahydropyran-4-yloxy)-3,4-dihydroquinazolin-4-one**

Obtained from 5, 7-difluoro-3,4-dihydroquinazoline (reference example 5) and tetrahydropyran-4-ol in 38% yield; NMR spectrum (CDCl₃) 1.92 (m, 2H), 2.08 (m, 2H), 3.64 (m, 2H), 4.10 (m, 2H), 4.70 (m, 1H), 6.67 (dd, 1H), 7.00 (dd, 1H), 8.00 (s, 1H); Mass spectrum MH⁺ 265.

Reference Example 7**5-(1-Methylpiperidin-4-yloxy)-3,4-dihydroquinazolin-4-one**

Sodium hydride (4.1 g, 60%) was added in portions to 4-hydroxy-1-methylpiperidine (10.7 g) in DMA (125 ml). The reaction was stirred at room temperature for 15 minutes, 50°C for 15 minutes then allowed to cool to room temperature. 5-Fluoro-3,4-dihydroquinazolin-4-one (5.1 g) was added in a single portion, and the mixture heated at 80°C for 2 hours. The reaction was cooled, concentrated *in vacuo* and the residue purified by chromatography using DCM - 7N ammonia in methanol (9:1) as eluent to give the title compound as a white solid after trituration with ether (7.3 g, 91%); NMR spectrum (DMSO-d₆) 1.72 (m, 2H), 1.88 (m, 2H), 2.15 (s, 3H), 2.19 (m, 2H), 2.63 (m, 2H), 4.46 (m, 1H), 7.00 (d, 1H), 7.14 (d, 1H), 7.61 (t, 1H), 7.91 (s, 1H), 11.75 (bs, 1H).

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The procedure described above was repeated using the appropriate alcohol. Thus was obtained the compound described below:

Reference Example 7.1

5-(1-*tert*-Butoxycarbonylpiperidin-4-yloxy)-3,4-dihydroquinazolin-4-one

- 5 Obtained from 1-*tert*-butoxycarbonyl-4-hydroxypiperidine in 87% yield; NMR spectrum (DMSO- d_6) 1.39 (s, 9H), 1.6 - 1.87 (m, 4H), 3.32 - 3.43 (m, 2H), 3.47 - 3.60 (m, 2H), 4.75 (m, 1H), 7.08 (d, 1H), 7.17 (d, 1H), 7.64 (t, 1H) 8.84 (s, 1H), 11.80 (bs, 1H); Mass spectrum MH^+ 346.

Reference Example 8

10 **5-Hydroxy-7-fluoro-3,4-dihydroquinazolin-4-one trifluoroacetate**

- Trifluoroacetic acid (50 ml) was added to 5-benzyloxy-7-fluoro-3,4-dihydroquinazolin-4-one (reference example 6) (1.64 g) and the resulting pale yellow solution was heated at 70°C for 2 hours. The reaction mixture was concentrated *in vacuo* to give an oil. Diethyl ether was added to give a solid which was filtered to afford the title compound as a pink solid (820 mg, 75%); NMR spectrum (DMSO- d_6) 6.72 (dd, 1H), 7.86 (dd, 1H), 8.12 (s, 1H), 12.13 (bs, 1H); Mass spectrum MH^+ 181.
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Reference Example 9

7-Benzyloxy-3,4-dihydro-5-hydroxyquinazolin-4-one

- Magnesium bromide (4.3 g) was added cautiously to 5, 7-dibenzyloxy-3,4-dihydroquinazolin-4-one (reference example 5.1) (8.37 g) in pyridine (250 ml) and the solution heated at reflux for 1 hour. The reaction mixture was cooled, concentrated *in vacuo* and the residue triturated with water and filtered to yield the title compound as an off-white solid (6.2 g, 99%); Mass spectrum MH^+ 269.
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- The procedure described above was repeated using the appropriate 5-alkoxyquinazoline. Thus was obtained the compound described below:
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Reference Example 9.1

3,4-Dihydro-5-hydroxy-7-methoxyquinazolin-4-one

Obtained from 3,4-dihydro-5,7-dimethoxyquinazolin-4-one (reference example 5.2) in 93% yield; Mass spectrum MH^+ 193.

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Reference Example 10**4-(3-Chloro-4-fluoroanilino)-5-hydroxy-7-methoxyquinazoline**

Pyridine hydrochloride (1.08 g) was added to 4-(3-chloro-4-fluoroanilino)-5,7-dimethoxyquinazoline (reference example 19.1) (3.29 g) suspended in pyridine (50 ml). The reaction was heated at 115°C for 8 hours then allowed to cool to room temperature. The precipitate formed upon cooling was filtered and washed with water before drying under suction to afford the title compound as a yellow solid (2.21 g, 70%); NMR spectrum (DMSO-d₆) 3.8 (s, 3H), 6.4 (d, 2H), 7.4 (t, 1H), 7.6 (m, 1H), 8.0 (d, 1H), 8.5 (s, 1H); Mass spectrum MH⁺ 320.

10 Reference Example 11**3,4-Dihydro-5-hydroxy-7-(3-(R)-dimethylaminopyrrolidin-1-yl)quinazolin-4-one**

3-(R)-(+)-Dimethylaminopyrrolidine (490 µl) was added to 3,4-dihydro-5-hydroxy-7-fluoroquinazolin-4-one trifluoroacetate (reference example 8) (400 mg) suspended in NMP (400 µl). The resulting solution was heated at 100°C for 3 hours. The reaction mixture was concentrated *in vacuo* to give a brown oil. Methanol (500 µl) was added and the suspension filtered to afford the title compound as a pink solid (243 mg, 41%); NMR spectrum (DMSO-d₆) 1.80 (m, 1H), 2.18 (s, 6H), 2.78 (m, 1H), 3.05 (dd, 1H), 3.24 (m, 2H), 3.47 (m, 2H), 6.00 (d, 1H), 6.10 (d, 1H), 7.88 (s, 1H), 11.85 (bs, 2H); Mass spectrum MH⁺ 273.

The procedure described above was repeated using the appropriate 7-fluoroquinazoline and amine. Thus was obtained the compound described below:

Reference Example 11.1**3,4-Dihydro-7-(3-(S)-dimethylaminopyrrolidin-1-yl)-5-(tetrahydropyran-4-yloxy)quinazolin-4-one**

Obtained from 3,4-dihydro-7-fluoro-5-(tetrahydropyranyl-4-oxy)quinazolin-4-one (reference example 6.1) and 3-(S)-dimethylaminopyrrolidine in 74% yield; NMR spectrum (DMSO-d₆) 1.66 (m, 2H), 1.90 (m, 2H), 2.20 (s, 6H), 2.77 (m, 1H), 3.07 (t, 1H), 3.26 (m, 3H), 3.40 – 3.58 (m, 4H), 3.90 (m, 2H), 4.65 (m, 1H), 6.20 (s, 2H), 7.75 (s, 1H); Mass spectrum MH⁺ 359.

Reference Example 12

30 7-(3-(R)-Dimethylaminopyrrolidin-1-yl)-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one

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Sodium hydride (40 mg) was added portionwise over 5 minutes to 3,4-dihydro-5-hydroxy-7-(3-(*R*)-dimethylaminopyrrolidin-1-yl)quinazolin-4-one (reference example 11) (0.24 g) in DMF (5 ml) at 0°C. Chloromethyl pivalate (130 µl) was added dropwise over 15 minutes to give a clear orange solution. The reaction mixture was allowed to warm to room temperature and stirred for a further 18 hours. Incomplete reaction was seen by tlc, therefore reaction was cooled to 0°C and sodium hydride (10 mg) was added followed by chloromethyl pivalate (26 µl). Reaction was complete after stirring for 1 hour at room temperature. The reaction mixture was concentrated *in vacuo* and purified by chromatography using 2-10% methanol in DCM as eluent to afford the title compound as a cream solid (210 mg, 62%);

10 NMR spectrum (DMSO-d₆) 1.10 (s, 9H), 1.83 (m, 1H), 2.22 (s, 6H), 2.81 (m, 1H), 3.13 (m, 1H), 3.33 (m, 2H), 3.45 - 3.60 (m, 2H), 5.80 (s, 2H), 6.08 (d, 1H), 6.18 (d, 1H), 8.21 (s, 1H), 11.39 (s, 1H); Mass spectrum MH⁺ 389.

The procedure described above was repeated using the appropriate 3,4-dihydroquinazolin-4-one. Thus were obtained the compounds described below:

15 Reference Example 12.1

5-Hydroxy-7-methoxy-3-pivaloyloxymethyl-quinazolin-4-one

Obtained from 3,4-dihydro-5-hydroxy-7-methoxyquinazolin-4-one (reference example 9.1) in 67% yield; NMR spectrum (DMSO-d₆) 1.11 (s, 9H), 3.85 (s, 3H), 5.86 (s, 2H), 6.51 (d, 1H), 6.66 (d, 1H), 8.37 (s, 1H), 11.42 (s, 1H); Mass spectrum M-H⁺ 305.

20 Reference Example 12.2

7-Benzoyloxy-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one

Obtained from 7-benzoyloxy-3,4-dihydro-5-hydroxyquinazolin-4-one (reference example 9) in 93% yield; NMR spectrum (DMSO-d₆) 1.11 (s, 9H), 5.23 (s, 2H), 5.86 (s, 2H), 6.59 (d, 1H), 6.74 (d, 1H), 7.29 - 7.47 (m, 5H), 8.37 (s, 1H), 11.42 (s, 1H); Mass spectrum M-H⁺ 383.

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Reference Example 13

7-(3-(*R*)-Dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one

7-(3-(*R*)-Dimethylaminopyrrolidin-1-yl)-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12) (210 mg), 4-hydroxy-*N*-methylpiperidine (125 mg) and triphenylphosphine (280 mg) were dissolved in anhydrous DCM (10 ml), under a nitrogen atmosphere at 0°C. A solution of di-*tert*-butyl azodicarboxylate (250 mg) in DCM (1

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ml) was added dropwise over 5 minutes and the resulting yellow solution was allowed to warm to room temperature and stirred for 18 hours. A further 1 equivalent of all reagents was added in the same sequence as above under the same reaction conditions and was left to stir for a further 12 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the residue purified by chromatography using 2-8% methanol in DCM as eluent to afford the title compound as a cream solid (200 mg, 77%); Mass spectrum MH^+ 486.

The procedure described above was repeated using the appropriate 5-hydroxyquinazoline and alcohol. Thus were obtained the compounds described below:

Reference Example 13.1

10 7-Methoxy-3-pivaloyloxymethyl-5-(tetrahydrofuran-3-yloxy)-3,4-dihydroquinazolin-4-one

Obtained from 5-hydroxy-7-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12.1) and tetrahydrofuran-3-ol in 80% yield; Mass spectrum MH^+ 377.

15 Reference Example 13.2

7-Methoxy-3-pivaloyloxymethyl-5-(tetrahydropyran-4-yloxy)-3,4-dihydroquinazolin-4-one

Obtained from 5-hydroxy-7-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12.1) and tetrahydropyran-4-ol in 70% yield; NMR spectrum (DMSO- d_6) 1.11 (s, 9H), 1.66 (m, 2H), 1.92 (m, 2H), 3.49 (m, 2H), 3.85 (s, 3H), 3.89 (m, 2H), 4.76 (m, 1H), 5.81 (s, 2H), 6.68 (s, 2H), 8.30 (s, 1H).

Reference Example 13.3

7-Benzoyloxy-3-pivaloyloxymethyl-5-(tetrahydropyran-4-yloxy)-3,4-dihydroquinazolin-4-one

25 Obtained from 7-benzoyloxy-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12.2) and tetrahydropyran-4-ol in 80% yield; Mass spectrum MH^+ 467.

Reference Example 13.4

30 7-Benzoyloxy-5-(1-methylpiperidin-4-yloxy)-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one

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Obtained from 7-benzyloxy-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12.2) and 1-methylpiperidin-4-ol in 100% yield; Mass spectrum MH⁺ 480.

Reference Example 13.5

5 7-Methoxy-5-(1-methylpiperidin-4-yloxy)-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one

Obtained from 5-hydroxy-7-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12.1) and 1-methylpiperidin-4-ol in 56% yield; NMR spectrum (DMSO-d₆) 1.11 (s, 9H), 1.71 (m, 2H), 1.87 (m, 2H), 2.13 (s, 3H), 2.18 (m, 2H), 2.57 (m, 10 2H), 3.84 (s, 3H), 4.52 (m, 1H), 5.79 (s, 2H), 6.61 (d, 1H), 6.67 (d, 1H), 8.16 (s, 1H); Mass spectrum MH⁺ 405.

Reference Example 13.6

7-Benzyloxy-3-pivaloyloxymethyl-5-(tetrahydrofuran-3-yloxy)-3,4-dihydroquinazolin-4-one

15 Obtained from 7-benzyloxy-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12.2) tetrahydrofuran-3-ol in 83% yield; Mass spectrum MH⁺ 454.

Reference Example 13.7

7-Benzyloxy-5-cyclopentyloxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one

Obtained from 7-benzyloxy-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12.2) and cyclopentanol in 88% yield; Mass spectrum MH⁺ 451.

Reference Example 14

3,4-Dihydro-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one

7N Ammonia in methanol (20 ml) was added to 7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 13) (200 mg) and the solution stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* to give an oil which was triturated with diethyl ether to give an orange solid which was filtered to afford the title compound (100 mg, 66%); NMR spectrum (DMSO-d₆) 1.72 (m, 3H), 1.87 (m, 3H), 2.10 (m, 3H), 2.15 (s, 3H), 2.18 (s, 6H), 2.63 (m, 2H), 2.75 (m, 1H), 3.05 (dd, 1H), 3.26 (m, 1H), 3.30 - 3.50 (m, 2H), 4.35 (m, 1H), 6.08 (s, 1H), 6.12 (s, 1H), 7.67 (s, 1H), 11.07 (bs, 1H); Mass spectrum MH⁺ 370.

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The procedure described above was repeated using the appropriate 3-pivaloyloxymethylquinazolinone. Thus were obtained the compounds described below:

Reference Example 14.1

3,4-Dihydro-7-methoxy-5-(tetrahydrofuran-3-yloxy)quinazolin-4-one

- 5 Obtained from 7-methoxy-3-pivaloyloxymethyl-5-(tetrahydrofuran-3-yloxy)-3,4-dihydroquinazolin-4-one (reference example 13.1) in 87% yield; Mass spectrum MH^+ 263.

Reference Example 14.2

3,4-Dihydro-7-methoxy-5-(tetrahydropyran-4-yloxy)quinazolin-4-one

- 10 Obtained from 7-methoxy-3-pivaloyloxymethyl-5-(tetrahydropyran-4-yloxy)-3,4-dihydroquinazolin-4-one (reference example 13.2) in 91% yield; NMR spectrum (DMSO-d₆) 1.65 (m, 2H), 1.91 (m, 2H), 3.48 (m, 2H), 3.83 (s, 3H), 3.89 (m, 2H), 4.70 (m, 1H), 6.60 (d, 2H), 6.65 (d, 2H), 7.88 (s, 1H), 12.12 (bs, 1H); Mass spectrum $M-H^+$ 275.

Reference Example 14.3

7-Benzoyloxy-3,4-dihydro-5-(tetrahydropyran-4-yloxy)quinazolin-4-one

- 15 Obtained from 7-benzoyloxy-3-pivaloyloxymethyl-5-(tetrahydropyran-4-yloxy)-3,4-dihydroquinazolin-4-one (reference example 13.3) in 76% yield; Mass spectrum MH^+ 263.

Reference Example 14.4

7-Benzoyloxy-3,4-dihydro-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one

- 20 Obtained from 7-benzoyloxy-5-(1-methylpiperidin-4-yloxy)-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 13.4) in 48% yield; Mass spectrum MH^+ 366.

Reference Example 14.5

3,4-Dihydro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one

- 25 Obtained from 7-methoxy-5-(1-methylpiperidin-4-yloxy)-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 13.5) in 75% yield; NMR spectrum (DMSO-d₆) 1.68 (m, 2H), 1.84 (m, 2H), 2.11 (s, 3H), 2.18 (m, 2H), 2.61 (m, 2H), 3.82 (s, 3H), 4.45 (m, 1H), 6.53 (d, 2H), 6.64 (d, 2H), 7.86 (s, 1H), 11.60 (bs, 1H); Mass spectrum MH^+ 290.

Reference Example 14.6

7-Benzoyloxy-3,4-dihydro-5-(tetrahydrofuran-3-yloxy)quinazolin-4-one

- 30 Obtained from 7-benzoyloxy-3-pivaloyloxymethyl-5-(tetrahydrofuran-3-yloxy)-3,4-dihydroquinazolin-4-one (reference example 13.6) in 86% yield; NMR spectrum (DMSO-d₆) 2.00 (m, 1H), 2.17 (m, 1H), 3.81 (m, 4H), 5.05 (m, 1H), 5.21 (s, 2H), 6.54 (d, 1H), 6.75 (d, 1H), 7.40 (m, 5H), 7.87 (s, 1H), 11.67 (bs, 1H); Mass spectrum MH^+ 339.

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Reference Example 14.7**7-Benzoyloxy-5-cyclopentyloxy-3,4-dihydroquinazolin-4-one**

Obtained from 7-benzoyloxy-5-cyclopentyloxy-3-pivaloyloxymethyl-3,4-dihydroquinazolinone (reference example 13.7) in 88% yield; Mass spectrum MH^+ 337.

5 Reference Example 15**5-(1-tert-Butoxycarbonylpiperidin-4-yloxy)-3,4-dihydro-7-methoxyquinazolin-4-one**

Di-tert-butylazodicarboxylate (915 mg) was added to a stirred solution of 5-hydroxy-7-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (reference example 12.1) (800 mg), 1-tert-butoxycarbonyl-4-hydroxypiperidine (631 mg), and triphenylphosphine (1.02 g) in dry DCM (13 ml), under an atmosphere of nitrogen. External cooling (ice bath) was applied during the addition. The reaction was then stirred for ten minutes, after which it was allowed to warm to room temperature. After 2 hours, the mixture was concentrated *in vacuo* to give the crude material as an orange oil. A solution of ammonia in methanol (7N) was added to this crude mixture, to give an orange solution, which was stirred at room temperature for 24 hours. The mixture was then concentrated *in vacuo*, and the residue purified by column chromatography, using 0-10% methanol in DCM, to give the title compound as white foam that solidified on drying overnight (892 mg, 91%); NMR spectrum ($CDCl_3$) 1.47 (s, 9H), 1.93 (m, 4 H), 3.54 (m, 2H) 3.70 (m, 2H), 3.90 (s, 3H), 4.66 (m, 1H), 6.50 (d, 1H), 6.77 (d, 1H), 7.89 (s, 1H), 10.32 (s, 1H); Mass spectrum $M-H^+$ 374.

20 Reference Example 16**4-Chloro-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one**

Phosphorus oxychloride (1.4 ml) was added to a solution of 3,4-dihydro-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one (reference example 14) (1.75 g) and di-isopropylethylamine (6.3 ml) in 1, 2-dichloroethane (100 ml), and the resulting solution heated at reflux for 3 hours. The reaction was cooled and concentrated *in vacuo* and the residue purified by chromatography using DCM-methanol-triethylamine (8:1:1) as eluent. The resulting solid was triturated with DCM and filtered. The filtrate was evaporated to yield the title compound as a yellow solid (1.5 g, 81%); Mass spectrum M^+ 390.

The procedure described above was repeated using the appropriate 3,4-dihydroquinazolin-4-one. Thus was obtained the compound described below:

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Reference Example 16.1**4-Chloro-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained from 3,4-dihydro-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one (reference example 7) in 66% yield; NMR spectrum (CDCl₃) 2.10 (m, 2H), 2.23 (m, 2H), 2.42 (s, 3H),
5 2.60 (m, 2H), 2.84 (m, 2H), 4.73 (m, 1H), 7.04 (d, 1H), 7.62 (d, 1H), 7.81 (t, 1H), 8.93 (s, 1H); Mass spectrum M⁺ 278.

Reference Example 16.2**4-Chloro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline**

Obtained from 3,4-dihydro-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one
10 (reference example 14.5) in 99% yield; NMR spectrum (CDCl₃) 2.10 (m, 4H), 2.35 (s, 3H), 2.44 (m, 2H), 2.74 (m, 2H), 3.95 (s, 3H), 4.58 (s, 1H), 6.60 (d, 1H), 6.94 (d, 1H), 8.80 (s, 1H); Mass spectrum MH⁺ 308.

Reference Example 16.3**5-(1-*tert*-Butoxycarbonylpiperidin-4-yloxy)-4-chloroquinazoline**

15 Obtained from 5-(1-*tert*-butoxycarbonylpiperidin-4-yloxy)-3,4-dihydroquinazoline (reference example 7.1) in 66% yield; NMR spectrum (DMSO-d₆) 1.38 (s, 9H), 1.58 - 1.90 (m, 4H), 3.30 - 3.60 (m, 4H), 4.82 (m, 1H), 7.14 - 7.28 (m, 2H), 7.74 (t, 1H), 8.33 (s, 1H).

Reference Example 17**4-Chloro-5-fluoroquinazoline hydrochloride**

20 To a suspension of 3,4-dihydro-5-fluoroquinazolin-4-one (0.5 g) in thionyl chloride (5 ml) was added DMF (0.2 ml). The mixture was heated at reflux under an atmosphere of nitrogen for 3 hours. The mixture was evaporated *in vacuo*, the residue re-suspended in dry toluene, and evaporated again. The residue was dried *in vacuo* to give the title compound as a pale yellow solid (634 mg, 95%), which was used without further manipulation.

Reference Example 18**4-(3-Chloro-4-fluoroanilino)-5-fluoroquinazoline hydrochloride**

DMF (1 ml) was added dropwise to 5-fluoro-3,4-dihydroquinazolin-4-one (1.00 g) in thionyl chloride (10 ml). The reaction was heated at 110°C for 18 hours to afford an orange solution. The reaction mixture was concentrated *in vacuo* to give an orange solid. This solid
30 was added portionwise to a flask containing ice (100 g) and saturated aqueous sodium hydrogen carbonate solution (50 ml), maintaining the internal temperature < 5°C and checking the solution remained basic. The aqueous mixture was then extracted with DCM (3

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x 100 ml), organic extracts were combined, dried (MgSO₄), and concentrated *in vacuo* to afford an orange solid. 3-Chloro-4-fluoroaniline (0.88 g) and 1N HCl in diethyl ether (6.09 ml) were added to the orange solid suspended in IPA (50 ml). The resulting mixture was heated at 100°C for 90 minutes then allowed to cool to room temperature. The solid was
5 filtered and washed with IPA (5 ml), then diethyl ether (20 ml) to afford the title compound, as a beige solid (1.37 g, 69%); Mass spectrum MH⁺ 292.

Reference Example 19

7-Benzylloxy-4-(3-chloro-4-fluoroanilino)-5-(tetrahydropyran-4-yloxy)quinazoline

Di-isopropylethylamine (2.27 ml) was added to 7-benzylloxy-3,4-dihydro-5-
10 (tetrahydropyran-4-yloxy)quinazolin-4-one (reference example 14.3) (638 mg) dissolved in anhydrous 1,2-dichloroethane (30 ml) and the resulting solution cooled to 0°C in an ice bath. Phosphorous oxychloride (0.51 ml) was added dropwise and the reaction heated at reflux for 3 hours. The reaction mixture was concentrated *in vacuo* to give an orange oil. 3-Chloro-4-fluoroaniline (99 mg) was added to this oil dissolved in IPA (15 ml), followed by di-
15 isopropylethylamine (0.16 ml). The resulting mixture was heated at reflux for 1.5 hours. The reaction mixture was cooled to room temperature, and the resulting solid filtered, washed with IPA, then diethyl ether and dried *in vacuo* to afford the title compound as a green solid (0.577 g, 67%); Mass spectrum MH⁺ 480.

The procedure described above was repeated using the appropriate 3,4-
20 dihydroquinazolin-4-one and aniline. Thus was obtained the compound described below:

Reference Example 19.1

4-(3-Chloro-4-fluoroanilino)-5, 7-dimethoxyquinazoline

Obtained from 3,4-dihydro-5,7-dimethoxyquinazolin-4-one (reference example 5.2) and 3-chloro-4-fluoroaniline in 92% yield; NMR spectrum (DMSO-d₆) 4.0 (s, 3H), 4.1 (s, 3H), 6.9-7.0 (dd, 2H), 7.5-7.6 (m, 2H), 7.9 (dd, 1H), 8.7 (s, 1H); Mass spectrum M-H⁺ 334.

Reference Example 19.2

7-Benzylloxy-4-(3-bromoanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained from 7-benzylloxy-3,4-dihydro-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one (reference example 14.4) and 3-bromoaniline in 38% yield; Mass spectrum MH⁺ 521.

Reference Example 19.3

7-Benzylloxy-4-(3-chloro-4-fluoroanilino)-5-(tetrahydrofuran-3-yloxy)quinazoline

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Obtained from 7-benzyloxy-3,4-dihydro-5-(tetrahydrofuran-3-yloxy)quinazolin-4-one (reference example 14.6) and 3-chloro-4-fluoroaniline in 34% yield; Mass spectrum MH^+ 466.

Reference Example 19.4

5 7-Benzyloxy-4-(3-chloro-4-fluoroanilino)-5-cyclopentyloxyquinazoline

Obtained from 7-benzyloxy-5-cyclopentyloxy-3,4-dihydroquinazolin-4-one (reference example 14.7) and 3-chloro-4-fluoroaniline in 47% yield; NMR spectrum (DMSO-d₆) 1.72 (m, 4H), 2.02 (m, 4H), 5.29 (m, 1H), 5.32 (s, 2H), 7.01 (d, 1H), 7.07 (d, 1H), 7.39 (m, 3H) 7.53 (m, 4H), 8.06 (m, 1H), 8.81 (s, 1H), 10.42 (bs, 1H); Mass spectrum MH^+ 464.

Reference Example 19.5

7-Benzyloxy-4-(3-chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained from 7-benzyloxy-3,4-dihydro-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one (reference example 14.4) and 3-chloro-4-fluoroaniline in 21% yield; NMR spectrum (DMSO-d₆) 2.3 (m, 2H), 2.4 (m, 1H), 2.7 (d, 3H), 3.2 (m, 2H), 3.3 (m, 1H), 3.5 (m, 2H), 5.1 (m, 1H), 5.3 (s, 2H), 7.1 (s, 2H), 7.4 (m, 3H), 7.5 (m, 3H), 7.6 (m, 1H), 8.0 (m, 1H), 8.8 (d, 1H); Mass spectrum MH^+ 493.

Reference example 19.6

7-Benzyloxy-4-(3-methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

20 Obtained from 7-benzyloxy-3,4-dihydro-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one (reference example 14.4) and 3-methylaniline in 32% yield; NMR spectrum (DMSO-d₆) 2.2 (m, 2H), 2.4 - 2.5 (m, 6H), 2.7 (m, 2H), 3.1 (m, 2H), 3.5 (m, 2H), 5.1 (m, 1H), 5.3 (s, 2H), 7.1 - 7.2 (m, 2H), 7.3 - 7.6 (m, 8H), 8.0 (m, 1H), 8.8 (m, 1H); Mass spectrum MH^+ 455.

Reference example 19.7

25 7-Benzyloxy-4-(3-chloroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained from 7-benzyloxy-3,4-dihydro-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one (reference example 14.4) and 3-chloroaniline in 26% yield; NMR spectrum (DMSO-d₆) 2.2 (m, 2H), 2.3 - 2.4 (m, 5H), 2.7 (m, 2H), 3.1 (m, 2H), 3.4 (m, 2H), 5.1 (m, 1H), 5.3 (s, 2H), 7.0 - 7.2 (m, 3H), 7.3 - 7.6 (m, 8H), 8.8 (m, 1H); Mass spectrum MH^+ 475.

30 Reference Example 19.8

7-Benzyloxy-4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-cyclopentyloxyquinazoline

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Obtained from 7-benzyloxy-5-cyclopentyl-3,4-dihydroquinazolin-4-one (reference example 14.7) and 3-chloro-4-(3-fluorobenzyloxy)aniline (reference example 28) in 62% yield; Mass spectrum MH^+ 570.

Reference Example 19.9

5 7-Benzyloxy-4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained by reacting 7-benzyloxy-3,4-dihydro-5-(1-methylpiperidin-4-yloxy)quinazolin-4-one (reference example 14.4) and 3-chloro-4-(3-fluorobenzyloxy)aniline (reference example 28) in 96% yield; Mass spectrum MH^+ 599.

10 Reference Example 19.10

7-Benzyloxy-4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)quinazoline

Obtained by reacting 7-benzyloxy-3,4-dihydro-5-(tetrahydropyran-4-yloxy)quinazolin-4-one (reference example 14.3) with 3-chloro-4-(3-

15 fluorobenzyloxy)aniline (reference example 28) in 70% yield; Mass spectrum MH^+ 585.

Reference Example 19.11

7-Benzyloxy-4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained by reacting 7-benzyloxy-3,4-dihydro-5-(tetrahydrofuran-3-yloxy)quinazolin-
20 4-one (reference example 14.3) with 3-chloro-4-(3-fluorobenzyloxy)aniline (reference example 28) in 70% yield; NMR spectrum (DMSO- d_6) 2.2 (m, 1H), 2.3 (m, 1H), 3.8 - 4.0 (m, 3H), 4.2 (d, 1H), 5.2 (s, 2H), 5.2 (s, 2H), 5.5 (m, 1H), 6.9 (d, 1H), 6.9 (d, 1H), 7.1 - 7.5 (m, 11H), 8.2 (d, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Mass spectrum MH^+ 572.

Reference Example 20

25 4-(3-Chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydropyran-4-yloxy)quinazoline trifluoroacetate

A mixture of 7-benzyloxy-4-(3-chloro-4-fluoroanilino)-5-(tetrahydropyran-4-yloxy)quinazoline (reference example 19) (0.58 g) and trifluoroacetic acid (25 ml) was heated at 70°C for 20 hours. The reaction mixture was cooled, concentrated *in vacuo*, and the
30 residue triturated with diethyl ether to give the title compound as a pale green solid (0.49 g, 82%); NMR spectrum (DMSO- d_6) 1.94 (m, 2H), 2.15 (m, 2H), 3.53 (t, 2H), 3.89 (m, 2H),

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4.96 (m, 1H), 6.81 (s, 1H), 6.92 (s, 1H), 7.50 (t, 1H), 7.57 (m, 1H), 8.09 (dd, 1H), 8.68 (s, 1H), 10.31 (s, 1H); Mass spectrum MH^+ 390.

The procedure described above was repeated using the appropriate 7-benzyloxyquinazoline. Thus were obtained the compounds described below:

5 Reference Example 20.1

4-(3-Bromoanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate

Obtained from 7-benzyloxy-4-(3-bromoanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 19.2) in 93% yield; Mass spectrum MH^+ 431.

Reference Example 20.2

10 4-(3-Chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydrofuran-3-yloxy)quinazoline trifluoroacetate

Obtained from 7-benzyloxy-4-(3-chloro-4-fluoroanilino)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 19.3) in 79% yield; Mass spectrum MH^+ 376.

Reference Example 20.3

15 4-(3-Chloro-4-fluoroanilino)-5-cyclopentyloxy-7-hydroxyquinazoline trifluoroacetate

Obtained from 7-benzyloxy-4-(3-chloro-4-fluoroanilino)-5-cyclopentyloxyquinazoline (reference example 19.4) in 60% yield; NMR spectrum (DMSO- d_6) 1.71 (m, 4H), 2.04 (m, 4H), 5.18 (m, 1H), 6.71 (d, 1H), 6.78 (d, 1H), 7.53 (m, 2H), 8.07 (m, 1H), 8.73 (s, 1H), 10.33 (bs, 1H); Mass spectrum MH^+ 374.

20 Reference Example 20.4

4-(3-Chloro-4-fluoroanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate

Obtained from 7-benzyloxy-4-(3-chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 19.5) in 93% yield; Mass spectrum MH^+ 403.

25 Reference Example 20.5

7-Hydroxy-4-(3-methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate

Obtained from 7-benzyloxy-4-(3-methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 19.6) in 80% yield; Mass spectrum $M-H^+$ 363.

30 Reference Example 20.6

4-(3-Chloroanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate

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Obtained from 7-benzyloxy-4-(3-chloroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 19.7) in 100% yield; Mass spectrum $M-H^+$ 383.

Reference Example 20.7

4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-5-cyclopentyloxy-7-hydroxyquinazoline

5 trifluoroacetate

Obtained from 7-benzyloxy-4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-cyclopentyloxyquinazoline (reference example 19.8) in 43% yield; Mass spectrum MH^+ 480.

Reference Example 20.8

4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-7-hydroxy-5-(1-methylpiperidin-4-

10 yloxy)quinazoline trifluoroacetate

Obtained from 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(1-methylpiperidin-4-yloxy)-7-benzyloxyquinazoline (reference example 19.9) in 27% yield; Mass spectrum MH^+ 509.

Reference Example 20.9

15 4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-7-hydroxy-5-(tetrahydropyran-4-yloxy)quinazoline trifluoroacetate

Obtained from 7-benzyloxy-4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)quinazoline (reference example 19.10) in 30% yield; Mass spectrum MH^+ 496.

20 Reference Example 20.10

4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-7-hydroxy-5-(tetrahydrofuran-3-yloxy)quinazoline trifluoroacetate

Obtained from 7-benzyloxy-4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 19.11) in > 100% yield; Mass spectrum MH^+ 482.

25 Reference Example 21

4-(3-Chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

Potassium carbonate (0.21 g) and 1-bromo-3-chloropropane (40 μ l) were added to a suspension of 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydrofuran-3-yloxy)quinazoline trifluoroacetate (reference example 20.2) (0.19 g) in DMF (4 ml). The mixture was stirred at room temperature for 23 hours, then more 1-bromo-3-chloropropane (19 μ l) was added and the mixture was stirred at room temperature for a further 18 hours. The mixture was then

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concentrated *in vacuo*, the residue was cooled and cold water was added. The resulting solid was filtered, washed with cold water and dried *in vacuo* to give the title compound as a green solid (0.15g, 88%); NMR spectrum (DMSO-d₆) 2.22 (m, 4H), 3.85 (m, 5H), 4.22 (m, 3H), 5.46 (m, 1H), 6.80 (d, 1H), 6.83 (d, 1H), 7.42 (t, 1H), 7.59 (m, 1H), 8.27 (m, 1H), 8.49 (s, 1H), 9.91 (s, 1H); Mass spectrum MH⁺ 452.

The procedure described above was repeated using the appropriate 7-hydroxyquinazoline and alkyl halide. Thus were obtained the compounds described below:

Reference Example 21.1

4-(3-Chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-cyclopentyloxyquinazoline

10 Obtained from 4-(3-chloro-4-fluoroanilino)-5-cyclopentyloxy-7-hydroxyquinazoline trifluoroacetate (reference example 20.3) and 1-bromo-3-chloropropane in 99% yield; NMR spectrum (DMSO-d₆) 1.72 (m, 4H), 2.01 (m, 4H), 2.22 (m, 2H), 3.81 (t, 2H), 4.23 (t, 2H), 5.17 (m, 1H), 6.70 (m, 1H), 6.79 (m, 1H), 7.44 (m, 2H), 8.25 (m, 1H), 8.47 (s, 1H), 9.88 (s, 1H); Mass spectrum MH⁺ 450.

15 Reference Example 21.2

4-(3-Chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained from 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate (reference example 20.4) and 1-bromo-3-chloropropane in 20 66% yield; Mass spectrum MH⁺ 479.

Reference Example 21.3

4-(3-Chloro-4-fluoroanilino)-7-(3-chloropropoxy)-5-(tetrahydropyran-4-yloxy)quinazoline

Obtained from 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydropyran-4-yloxy)quinazoline trifluoroacetate (reference example 20) and 1-bromo-3-chloropropane in 25 77% yield; Mass spectrum MH⁺ 467.

Reference Example 21.4

4-(3-Chloro-4-fluoroanilino)-7-(2-chloroethoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained from 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydrofuran-3-yloxy)quinazoline trifluoroacetate (reference example 20.2) and 1-bromo-2-chloroethane in 30 90% yield; NMR spectrum (DMSO-d₆) 2.17 (m, 1H), 2.32 (m, 1H), 3.78 - 4.01 (m, 5H), 4.18

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(d, 1H), 4.42 (t, 2H), 5.50 (m, 1H), 6.84 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.92 (s, 1H); Mass spectrum MH^+ 438.

Reference Example 21.5

7-(2-Chloroethoxy)-4-(3-chloro-4-fluoroanilino)-5-cyclopentyloxyquinazoline

- 5 Obtained from 4-(3-chloro-4-fluoroanilino)-5-cyclopentyloxy-7-hydroxyquinazoline trifluoroacetate (reference example 20.3) and 1-bromo-2-chloroethane in 75% yield; NMR spectrum (DMSO- d_6) 1.72 (m, 4H), 2.01 (m, 4H), 3.99 (m, 2H), 4.41 (m, 2H), 5.21 (m, 1H), 6.72 (m, 1H), 6.81 (m, 1H), 7.45 (m, 2H), 8.25 (m, 1H), 8.48 (s, 1H), 9.88 (s, 1H); Mass spectrum MH^+ 436.

10 Reference Example 21.6

7-(2-Chloroethoxy)-4-(3-chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

- Obtained from 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate (reference example 20.4) and 1-bromo-2-chloroethane in 53% yield; Mass spectrum MH^+ 465.

Reference Example 21.7

7-(2-Chloroethoxy)-4-(3-chloro-4-fluoroanilino)-5-(tetrahydropyran-4-yloxy)quinazoline

- Obtained from 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydropyran-4-yloxy)quinazoline trifluoroacetate (reference example 20) and 1-bromo-2-chloroethane in 85% yield; Mass spectrum MH^+ 452.

Reference Example 21.8

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-chloropropoxy)-5-cyclopentyloxyquinazoline

- Obtained from 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-cyclopentyloxy-7-hydroxyquinazoline trifluoroacetate (reference example 20.7) and 1-bromo-3-chloropropane in 100% yield; NMR spectrum (DMSO- d_6) 1.60 - 1.82 (m, 4H), 1.90 - 2.15 (m, 4H), 2.22 (m, 2H), 3.82 (t, 2H), 4.23 (t, 2H), 5.18 (m, 1H), 5.23 (s, 2H), 6.68 (d, 1H), 6.78 (d, 1H), 7.17 (m, 1H), 7.25 (m, 3H), 7.43 (m, 2H), 8.13 (d, 1H), 8.42 (s, 1H), 9.80 (s, 1H); Mass spectrum MH^+ 556.

30 Reference Example 21.9

7-(2-Chloroethoxy)-4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-cyclopentyloxyquinazoline

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Obtained from 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-cyclopentyloxy-7-hydroxyquinazoline trifluoroacetate (reference example 20.7) and 1-bromo-2-chloroethane in 100% yield; Mass spectrum MH^+ 542.

Reference Example 21.10

5 4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-chloropropoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline

Obtained from 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline (reference example 20.8) and 1-bromo-3-chloropropane in 78% yield; Mass spectrum MH^+ 585.

10 Reference Example 21.11

7-(2-Chloroethoxy)-4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydropyran-4-yloxy)quinazoline

Obtained from 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-7-hydroxy-5-(tetrahydropyran-4-yloxy)quinazoline (reference example 20.9) and 1-bromo-2-chloroethane
15 in 83% yield; Mass spectrum MH^+ 558.

Reference Example 21.12

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-chloropropoxy)-5-(tetrahydropyran-4-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzoyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-hydroxyquinazoline (reference example 20.9) and 1-bromo-3-chloropropane in
20 100% yield; NMR spectrum ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 4H), 2.8 (t, 4H), 3.6 (m, 2H), 3.8 (t, 2H), 4.1 (dt, 2H), 4.2 (t, 2H), 4.8 (m, 1H) 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Mass spectrum MH^+ 572.

25 Reference Example 21.13

4-(3-Chloro-4-(3-fluorobenzoyloxy)anilino)-7-(3-chloropropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline

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Obtained by reacting 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-hydroxyquinazoline (reference example 20.10) and 1-bromo-3-chloropropane in 91% yield; NMR spectrum (DMSO-d₆) 2.1 - 2.4 (m, 4H), 3.8-4.0 (m, 5H), 4.2 - 4.3 (m, 3H), 5.2 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.1-7.3 (m, 4H), 7.4 - 7.5 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Mass spectrum MH⁺ 558.

Reference Example 21.14

7-(2-Chloroethoxy)-4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained by reacting 4-(3-chloro-4-(3-fluorobenzyloxy)anilino)-5-(tetrahydropyran-4-yloxy)-7-hydroxyquinazoline (reference example 20.10) and 1-bromo-2-chloroethane in 100% yield; NMR spectrum (DMSO-d₆) 2.2 (m, 1H), 2.3 (m, 1H), 3.8 - 4.0 (m, 5H), 4.2 (d, 1H), 4.4 (t, 2H), 5.2 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.1-7.3 (m, 4H), 7.4 - 7.5 (m, 2H), 8.2 (m, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Mass spectrum MH⁺ 544.

Reference Example 22

7-(1-tert-Butoxycarbonylpiperidin-4-ylmethoxy)-4-(3-chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

Potassium carbonate (240 mg) was added to 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate (reference example 20.4) (175 mg) in DMA (5 ml). 1-(tert-Butoxycarbonyl)-4-tosyloxymethylpiperidine (reference example 41) (161 mg) was added and the resulting mixture was stirred for 18 hours at room temperature. The reaction was then heated at 60°C for 18 hours and the solvent concentrated *in vacuo* to give a solid. Water was added to this and the solid filtered to afford the title compound as a beige solid (100 mg, 38%); NMR spectrum (DMSO-d₆) 1.2 (m, 2H), 1.4 (s, 9H), 1.5 (m, 1H), 1.7 (m, 2H), 1.9 (m, 2H), 2.1 (m, 2H), 2.2 (s, 3H), 2.2 (m, 2H), 3.8 (m, 2H), 4.0 (m, 4H), 4.8 (m, 1H), 6.8 (s, 2H), 7.4 (m, 2H), 7.6 (m, 1H), 7.8 (d, 1H), 8.2 (dd, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Mass spectrum MH⁺ 600.

The procedure described above was repeated using the appropriate 7-hydroxyquinazoline. Thus was obtained the compound described below:

Reference Example 22.1

7-(1-tert-Butoxycarbonylpiperidin-4-ylmethoxy)-4-(3-chloroanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline

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Obtained from 4-(3-chloroanilino)-7-hydroxy-5-(1-methylpiperidin-4-yloxy)quinazoline trifluoroacetate (reference example 20.6) in 35% yield; Mass spectrum MH^+ 582.

Reference Example 22.2

5 7-(1-*tert*-Butoxycarbonylpiperidin-4-ylmethoxy)-4-(3-chloro-4-fluoroanilino)-5-(tetrahydrofuran-3-yloxy)quinazoline

Obtained from 4-(3-chloro-4-fluoroanilino)-7-hydroxy-5-(tetrahydrofuran-3-yloxy)quinazoline (reference example 20.2) in 86% yield; Mass spectrum MH^+ 574.

Reference Example 23

10 *N*-*tert*-Butoxycarbonyl-3,5-dibenzyloxyaniline

Di-*isopropylethylamine* (6 ml) and diphenylphosphoryl azide (7 ml) were added to a suspension of 3, 5-dibenzyloxybenzoic acid (10 g) in *tert*-butanol (150 ml), and the reaction stirred at 70°C for 5 hours. The reaction was cooled, concentrated *in vacuo* and the residue purified by chromatography (isohexane-5% ethyl acetate) to give the title compound as a

15 white solid (5.8 g, 48%); NMR spectrum (DMSO- d_6) 1.43 (s, 9H), 5.00 (s, 4H), 6.30 (s, 1H), 6.80 (s, 1H), 7.10 - 7.42 (m, 10H), 9.24 (s, 1H); Mass spectrum $M-H^+$ 404.

Reference Example 24

3,5-Dibenzyloxyaniline trifluoroacetate

Trifluoroacetic acid (20 ml) was added to a solution of 3,5-dibenzyloxy-*N*-*tert*-butoxycarbonylaniline (reference example 23) (5.75 g) in DCM (150 ml) and the reaction stirred for 4 hours. The reaction was concentrated *in vacuo* to yield the title compound as a beige solid (7.4 g, >100%); Mass spectrum MH^+ 306. Alternatively, the product could be isolated as the hydrochloride salt by partitioning between saturated aqueous sodium bicarbonate and ethyl acetate, and acidification of the organic extracts by addition of a 1M

25 HCl solution in ether.

Reference Example 25

5-Amino-3-bromoindazole

Titanium trichloride (10% solution in HCl, 45 ml) was added dropwise to a solution of ammonium acetate (6.36 g) and 3-bromo-5-nitroindazole (obtained as described in *Eur. J. Med. Chem.*, (1986), 21(4), 359-362) (1.0 g) in a mixture of acetone (60 ml) and water (10 ml). The mixture was stirred at room temperature for 30 minutes before pouring into water (150 ml) and neutralising with 10N sodium hydroxide. The aqueous mixture was then

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extracted with ethyl acetate (3 x 100 ml), organic extracts were washed with saturated brine, then combined, dried and concentrated *in vacuo* to give the title compound as a pale pink solid (0.76 g, 86%); NMR spectrum (DMSO-d₆) 5.12 (bs, 2H), 6.54 (s, 1H), 6.83 (d, 1H), 6.86 (d, 1H), 12.88 (bs, 1H); Mass spectrum MH⁺ 212.

- 5 The procedure described above was repeated using the appropriate aryl nitro compound. Thus were obtained the compounds described below:

Reference Example 25.1

5-Amino-3-chloroindazole

Obtained from 3-chloro-5-nitroindazole in 87% yield; NMR spectrum (DMSO-d₆)

- 10 4.99 (bs, 2H), 6.58 (m, 1H), 6.83 (d, 1H), 6.86 (d, 1H), 12.71 (bs, 1H).

Reference Example 25.2

5-Amino-3-bromoindole

Obtained from 3-bromo-5-nitroindole (reference example 30.1) in 80% yield; NMR spectrum (DMSO-d₆) 5.48 (bs, 2H), 6.61 (m, 2H), 7.15 (d, 1H), 7.32 (d, 2H), 10.99 (s, 1H);

- 15 Mass spectrum MH⁺ 211.

Reference Example 26

5-Amino-3-chloro-1-(2-pyridylmethyl)indole

A solution of 3-chloro-5-nitro-1-(2-pyridylmethyl)indole (reference example 33) (2.5 g) in ethanol (130 ml) was stirred at room temperature. Sodium dithionite (7.6 g) in water (18

- 20 ml) was added, and the mixture was heated to 50°C for 5 hours, then cooled to room temperature. The ethanol was removed *in vacuo*, and the residue was partitioned between DCM and water. The DCM layer was separated, dried over sodium sulphate, then concentrated *in vacuo* to give the crude material, which was purified by chromatography using 50% DCM in isohexane then DCM as eluent to give the title compound as an orange
25 solid (488 mg, 23%); NMR spectrum (CDCl₃) 3.53 (s, 2H), 5.27 (s, 2H), 6.61 (dd, 1H), 6.68 (d, 1H), 6.86 (d, 1H), 7.01 (d, 1H), 7.04 (s, 1H), 7.11 (dd, 1H), 7.47 (dt, 1H), 8.55 (m, 1H); Mass spectrum MH⁺ 258.

The procedure described above was repeated using the appropriate aryl nitro compound. Thus were obtained the compounds described below:

- 30 Reference Example 26.1

5-Amino-3-chloro-1-(2-pyridylmethyl)indazole

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Obtained from 3-chloro-5-nitro-1-(2-pyridylmethyl)indazole (reference example 33.1) in 24% yield; NMR spectrum (CDCl₃) 3.3 (bs, 2H), 6.65 (dd, 1H), 6.77 (m, 1H), 6.84 - 7.02 (m, 5H), 7.24 (m, 1H).

Reference Example 26.2

5 5-Amino-3-chloroindole

Obtained from 3-chloro-5-nitroindole (reference example 30) in 17% yield; NMR spectrum (DMSO-d₆) 4.7 - 4.9 (bs, 2H), 6.6 (m, 2H), 7.1 (d, 1H), 7.2 (d, 1H).

Reference Example 26.3

3-Fluoro-4-(1-methyl-1H-imidazol-2-ylthio)aniline

10 Obtained from 3-fluoro-4-(1-methyl-1H-imidazol-2-ylthio)nitrobenzene (reference example 43) in 86% yield; Mass spectrum MH⁺ 224.

Reference Example 27

5-Amino-3-methylbenzothiazole

15 3-Methyl-5-nitrobenzothiazole (1 g) and 10% Pd/C (0.3 g) in ethanol (40 ml) were stirred for 16 hours under an atmosphere of hydrogen. The solid residues were removed by filtration and the solution concentrated *in vacuo*. The residue was triturated with ether and filtered to give the title compound as a pale yellow solid (0.25 g, 30% yield); NMR spectrum (DMSO-d₆) 2.52 (s, 3H), 5.30 (bs, 2H), 6.95 (dd, 1H), 7.03 (dd, 1H), 7.70 (d, 1H).

The procedure described above was repeated using the appropriate nitro compound.

20 Thus was obtained the compound described below:

Reference Example 27.1

5-Amino-3-methylindole

Obtained from 3-methyl-5-nitroindole (reference example 31) in 66% yield; NMR spectrum (DMSO-d₆) 2.1 (s, 3H), 4.4 (bs, 2H), 6.4 (dd, 1H), 6.6 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H); Mass spectrum MH⁺ 147.

Reference Example 27.2

5-Aminoindole-3-carbonitrile

Obtained from 5-nitroindole-3-carbonitrile (reference example 38) in 71% yield; NMR spectrum (DMSO-d₆) 4.8 (bs, 2H), 6.6 (dd, 1H), 6.7 (s, 1H), 7.2 (d, 1H), 7.9 (s, 1H); Mass spectrum MH⁺ 158.

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Reference Example 28**3-Chloro-4-(3-fluorobenzoyloxy)aniline**

- 5 To a solution of 2-chloro-1-(3-fluorobenzoyloxy)-4-nitrobenzene (reference example 34) (3.74 g) in ethyl acetate (60 ml) was added 10% Pt/C (0.5 g). The resulting solution was subjected to a hydrogen atmosphere for 4 hours at room temperature. The catalyst was then filtered off and the solvent concentrated *in vacuo* to give the title compound as an orange crystalline solid (3.08 g, 92%); NMR spectrum (DMSO-d₆) 4.91 (s, 2H), 5.01 (s, 2H), 6.45
10 (dd, 1H), 6.63 (s, 1H), 6.89 (d, 1H), 7.12 (t, 1H), 7.24 (t, 2H), 7.40 (m, 1H); Mass spectrum MH⁺ 252.

Reference Example 29**4-(Azepan-1-ylcarbonyl)-3-chloroaniline**

- To 1-(2-chloro-4-nitrobenzoyl)azepane (reference example 37) (2.58 g) was added
15 ethyl acetate (100 ml) and tin (II) chloride dihydrate (9 g). This was heated to 70°C for 4 hours, then allowed to cool. The mixture was made basic with 880 ammonia solution, the resulting solid filtered. The filtrate was extracted with water and combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by chromatography using DCM - 30% ethyl acetate as eluent to give the title compound as a white solid (1.85 g, 73%);
20 NMR spectrum (CDCl₃) 1.48 - 1.74 (m, 6H), 1.74 - 1.92 (m, 2H), 3.23 - 3.33 (m, 2H), 3.35 - 3.84 (m, 2H), 3.85 (s, 2H), 6.54 (dd, 1H), 6.68 (d, 1H), 7.02 (d, 1H); Mass spectrum MH⁺ 253.

Reference Example 30**3-Chloro-5-nitroindole**

- 25 *N*-Chlorosuccinimide (1.65 g) was added in portions to a solution of 5-nitroindole (2.00 g) in DMF (20 ml). The resulting solution was stirred at room temperature for 18 hours. The pale brown solution was poured into water (200 ml) to give a yellow precipitate which was filtered, washed with water and dried *in vacuo* to give the title compound as a yellow solid (2.40 g, 99%). Mass spectrum M-H⁺ 195.
30 The procedure described above was repeated using the appropriate *N*-halosuccinimide. Thus was obtained the compound described below:

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Reference Example 30.1**3-Bromo-5-nitroindole**

Obtained from *N*-bromosuccinimide in 89% yield; NMR spectrum (DMSO-d₆) 7.60 (d, 1H), 7.82 (d, 1H), 8.04 (dd, 1H), 8.30 (d, 1H), 12.16 (bs, 1H).

5 Reference Example 31**3-Methyl-5-nitroindole**

Tetra-*n*-butylammonium bromide (1.25 g) and triethylamine (1.37 ml) were added to allyl-(2-bromo-4-nitrophenyl)amine (reference example 32) (1.00 g) dissolved in DMF (5 ml). Palladium (II) acetate (50 mg) was added and the reaction was stirred at room
10 temperature for 72 hours. The reaction was filtered through celite after dilution with ethyl acetate. The solution was washed with water (50 ml), 5% aqueous HCl (50 ml), brine (50 ml) and dried. Concentration *in vacuo* gave a brown solid which was purified by chromatography using DCM as eluent to afford the title compound as a yellow solid (680 mg, 99%); NMR spectrum (DMSO-d₆) 2.3 (s, 3H), 7.4 (d, 1H), 7.5 (d, 1H), 8.0 (dd, 1H), 8.5 (d, 1H); Mass
15 spectrum M-H⁺ 175.

Reference Example 32**Allyl-(2-bromo-4-nitrophenyl)amine**

Potassium *tert*-butoxide (2.71 g) was added to 2-bromo-4-nitroaniline (5.00g) in DMF (30 ml) at 0°C. The resulting red solution was stirred at this temperature for 30 minutes. Allyl
20 bromide (2.05 ml) was added dropwise and the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was poured into 20% NaH₂PO₄ and extracted with ethyl acetate. The combined organic extracts were dried, filtered and concentrated *in vacuo* to afford an orange oil. This was purified by chromatography using ethyl acetate / isohexane (1:9) as eluent to afford the title compound as a yellow crystalline solid (2.25 g, 38%); NMR
25 spectrum (DMSO-d₆) 4.0 (m, 2H), 5.1 (d, 1H), 5.2 (dd, 1H), 5.9 (m, 1H), 6.7 (d, 1H), 6.9 (t, 1H), 8.0 (dd, 1H), 8.3 (d, 1H).

Reference Example 33**3-Chloro-5-nitro-1-(2-pyridylmethyl)indole**

2-Picolyl chloride hydrochloride (3.26 g) was added to a stirred mixture of 3-chloro-5-
30 nitroindole (reference example 30) (1.97 g) and potassium carbonate (13.8 g) in DMF (50 ml). The mixture was heated to 50°C and stirred for 2 hours, after which time the solvent was removed *in vacuo*. The residue was dissolved in DCM, then washed with water, and dried

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over sodium sulphate. Concentration gave the product as a yellow solid (2.53 g, 88%); NMR spectrum (CDCl₃) 5.43 (s, 2H), 6.90 (d, 1H), 7.23 (dd, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 7.62 (dt, 1H), 8.12 (dd, 1H), 8.60 (m, 2H).

The procedure described above was repeated using the appropriate heterocycle and
5 alkyl halide. Thus were obtained the compounds described below:

Reference Example 33.1

3-Chloro-5-nitro-1-(2-pyridinylmethyl)indazole

Obtained from 3-chloro-5-nitroindazole and 2-picolyl chloride hydrochloride in 74%
yield; NMR spectrum (CDCl₃) 5.32 (s, 2H), 6.80 (d, 1H), 6.89 (d, 1H), 7.01 (dt, 1H), 7.28 (m,
10 3H), 8.12 (dd, 1H), 8.61 (d, 1H).

Reference Example 34

2-Chloro-1-(3-fluorobenzoyloxy)-4-nitrobenzene

To a solution of 2-chloro-4-nitrophenol (20.0 g) in acetone (400 ml) was added
potassium carbonate (47.76 g) followed by the dropwise addition of 3-fluorobenzyl bromide
15 (32.67 g) over 15 minutes. The reaction mixture was then stirred at room temperature for 16
hours and filtered to remove insoluble material. The solvent was then concentrated *in vacuo*
and the solid remaining was purified by chromatography using 30-80% DCM / isohexane as
eluent to give the title compound (30.96 g, 95%); NMR spectrum (DMSO-d₆) 5.39 (s, 2H),
7.18 (t, 1H), 7.30 (m, 2H), 7.45 (m, 2H), 8.23 (dd, 1H), 8.32 (d, 1H); Mass spectrum M-H⁺
20 280.

The procedure described above was repeated using the appropriate phenol and alkyl
halide. Thus were obtained the compounds described below:

Reference Example 34.1

4-(2-Fluorobenzoyloxy)-3-iodonitrobenzene

25 Obtained from 2-fluorobenzyl bromide and 4-hydroxy-3-iodonitrobenzene in 85%
yield; Mass spectrum M-H⁺ 372.

Reference Example 34.2

4-(3-Fluorobenzoyloxy)-3-iodonitrobenzene

Obtained by reacting 4-hydroxy-3-iodonitrobenzene and 3-fluorobenzyl bromide in
30 99% yield; Mass spectrum M-H⁺ 372.

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Reference Example 35**4-(2-Fluorobenzyloxy)-3-(trimethylsilylethynyl)nitrobenzene**

To a solution of 4-(2-fluorobenzyloxy)-3-iodonitrobenzene (0.49 g) (reference
5 example 34.1) in acetonitrile (10 ml) was added trimethylsilylacetylene (0.54 ml), copper(I)
iodide (5 mg), bis(triphenylphosphine)-dichloropalladium (18 mg) and triethylamine (10 ml)
under nitrogen and the mixture stirred at room temperature for 4 hours. The reaction was
concentrated *in vacuo* and the residue purified by chromatography using DCM as eluent to
give the title compound as a yellow solid (0.33 g, 73%); Mass spectrum M-H⁺ 342.

10 The procedure described above was repeated using the appropriate halobenzene. Thus
were obtained the compounds described below:

Reference Example 35.1**4-(3-Fluorobenzyloxy)-3-(trimethylsilylethynyl)nitrobenzene**

Obtained from 4-(3-fluorobenzyloxy)-3-iodonitrobenzene (reference example 34.2);
15 Mass spectrum M-H⁺ 342.

Reference Example 36**4-Hydroxytetrahydrothiopyran**

Sodium borohydride (60 mg) was added to 2M NaOH (100 µl) and the resulting
solution diluted with water (0.75 ml). This solution was added dropwise to
20 tetrahydrothiopyran-4-one (0.5 g) in methanol (5 ml) using an ice bath to maintain the internal
temperature at 18-25°C. A further 0.13 equivalents of sodium borohydride was added and
after stirring at room temperature for 30 minutes the reaction was concentrated *in vacuo* to a
minimum volume and water (5 ml) was added. The solution was extracted with diethyl ether
(6 x 20ml), dried and concentrated *in vacuo* to afford the title compound as a colourless oil
25 (0.48 g, 94%); NMR spectrum (DMSO-d₆) 1.5 (m, 2H), 2.0 (m, 2H), 2.4 (m, 2H), 2.7 (m,
2H), 3.4 (m, 1H), 4.6 (d, 1H).

Reference Example 37**1-(2-Chloro-4-nitrobenzoyl)azepane**

To a solution of 2-chloro-5-nitrobenzoic acid (4.02 g) and triethylamine (2.20 g) in
30 DCM (150 ml) was added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium
hexafluorophosphate (8.36 g). This mixture was stirred at room temperature under an
atmosphere of nitrogen for 3 hours. Hexamethyleneimine (2.18 g) was added and this mixture

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stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue purified by chromatography using 0-10% ethyl acetate in DCM as eluent to give the title compound as a colourless oil which crystallised upon standing (5.09 g, 90%); NMR spectrum (CDCl₃) 1.53 - 1.77 (m, 6H), 1.79 - 1.93 (m, 2H), 3.15 - 3.27 (m, 2H), 3.60 - 3.84 (m, 2H),

5 7.48 (d, 1H), 8.18 (dd, 1H), 8.30 (d, 1H); Mass spectrum MH⁺ 283.

Reference Example 38

5-Nitroindole-3-carbonitrile

5-Nitroindole (2 g) was dissolved in diethyl ether (100 ml) and cooled to -10°C. Chlorosulphonyl isocyanate (5.37 ml) was added dropwise maintaining an internal
10 temperature of -10°C to afford a white precipitate. This was filtered and washed with ether before adding to DMF (100 ml). The resulting solution was stirred at room temperature for 1 hour, then poured into water (500 ml) to give a yellow solid, which was filtered and dried. This solid was stirred in ethyl acetate (250 ml) for 30 minutes, then filtered. The filtrate was evaporated *in vacuo* to afford the title compound as a pale yellow solid (1.35 g, 60%); NMR
15 spectrum (DMSO-d₆) 7.7 (d, 1H), 8.2 (dd, 1H), 8.5 (m, 2H); Mass spectrum M-H⁺ 186.

Reference Example 39

Ethyl 4-(1-(tert-butoxycarbonyl)piperidine)carboxylate

While maintaining the temperature in the range 0-5°C, a solution of di-*tert*-butyl dicarbonate (41.7 g) in ethyl acetate (75 ml) was added in portions to a solution of ethyl 4-
20 piperidinecarboxylate (30 g) in ethyl acetate (150 ml) cooled at 5°C. After stirring for 48 hours at ambient temperature, the mixture was poured into water (300 ml). The organic layer was separated, washed successively with water (200 ml), 0.1N aqueous hydrochloric acid (200 ml), saturated aqueous sodium hydrogen carbonate (200 ml) and brine (200 ml), dried and evaporated to give the title compound (48 g, 98%); NMR spectrum (CDCl₃) 1.25 (t, 3H),
25 1.45 (s, 9H), 1.55 - 1.70 (m, 2H), 1.8 - 2.0 (d, 2H), 2.35 - 2.5 (m, 1H), 2.7 - 2.95 (t, 2H), 3.9 - 4.1 (bs, 2H), 4.15 (q, 2H).

Reference Example 40

1-(tert-Butoxycarbonyl)-4-hydroxymethylpiperidine

A solution of 1M lithium aluminium hydride in THF (133 ml) was added in portions
30 to a solution of ethyl 4-(1-(tert-butoxycarbonyl)piperidine)carboxylate (reference example 39) (48 g) in dry THF (180 ml) cooled at 0°C. After stirring at 0°C for 2 hours, water (30 ml) was added followed by 2N sodium hydroxide (10 ml). The precipitate was removed by

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filtration through diatomaceous earth and washed with ethyl acetate. The filtrate was washed with water, brine, dried and evaporated to give the title compound (36.3 g, 89%); NMR spectrum (CDCl₃) 1.05 - 1.2 (m, 2H), 1.35 - 1.55 (m, 10H), 1.6 - 1.8 (m, 2H), 2.6 - 2.8 (t, 2H), 3.4 - 3.6 (t, 2H), 4.0 - 4.2 (bs, 2H); Mass spectrum M⁺ 215.

5 Reference Example 41

1-(tert-Butoxycarbonyl)-4-tosyloxymethylpiperidine

1, 4-Diazabicyclo[2.2.2]octane (42.4 g) was added to a solution of 1-(tert-butoxycarbonyl)-4-hydroxymethylpiperidine (reference example 40) (52.5 g) in *tert*-butyl methyl ether (525 ml). After stirring for 15 minutes at ambient temperature, the mixture was
10 cooled to 5°C and a solution of 4-toluenesulphonyl chloride (62.8 g) in *tert*-butyl methyl ether (525 ml) was added in portions over 2 hours while maintaining the temperature at 0°C. After stirring for 1 hour at ambient temperature, petroleum ether (1 l) was added. The precipitate was removed by filtration. The filtrate was evaporated to give a solid. The solid was
15 dissolved in ether and washed successively with 0.5N aqueous hydrochloric acid (2 x 500 ml), water, saturated aqueous sodium hydrogen carbonate and brine, dried and evaporated to give the title compound as a white solid (76.7 g, 85%); NMR spectrum (CDCl₃) 1.0 - 1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75 - 1.9 (m, 2H), 2.45 (s, 3H), 2.55 - 2.75 (m, 2H), 3.85 (d, 1H), 4.0 - 4.2 (bs, 2H), 7.35 (d, 2H), 7.8 (d, 2H); Mass spectrum M+Na⁺ 392.

Reference Example 42

20 3-Ethynyl-4-(2-fluorobenzyloxy)aniline

A solution of 4-(2-fluorobenzyloxy)-3-(trimethylsilylethynyl)nitrobenzene (310 mg) (reference example 35) and 10% Pt/C in ethyl acetate / ethanol (9:1, 10 ml) was stirred under an atmosphere of hydrogen for 20 minutes. The catalyst was removed by filtration and the solution concentrated *in vacuo* to give a green solid. This was dissolved in methanol (100 ml)
25 and DCM (50 ml), potassium carbonate (0.375 g) added and the solution stirred for 30 minutes. The reaction was filtered and concentrated *in vacuo*. The residue was purified by chromatography using DCM as eluent to give the title compound as a yellow oil (0.13 g, 62%); Mass spectrum MH⁺ 283.

The procedure described above was repeated using the appropriate nitrobenzene. Thus
30 was obtained the compound described below:

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Reference Example 42.1**3-Ethynyl-4-(3-fluorobenzoyloxy)aniline**

Obtained from 4-(3-fluorobenzoyloxy)-3-(trimethylsilyl)ethynyl)nitrobenzene (reference example 35.1); Mass spectrum MH^+ 283.

5 Reference Example 43**3-Fluoro-4-(1-methyl-1H-imidazolyl-2-ylthio)nitrobenzene**

To a stirred solution of 2-mercapto-1-methylimidazole (1.14 g), in DMF (20 ml), was added sodium hydride (0.44 g) in small portions and the reaction stirred at ambient temperature until effervescence ceased. To this was added a solution of 3,4-

10 difluoronitrobenzene (1.59 g) in DMF (10 ml), and the solution stirred at 80°C for 4 hours.

The reaction was poured into water (150 ml) and organic material extracted into ethyl acetate (150 ml). The organic layer was washed successively with water (3 x 150 ml), brine (150 ml) and dried. Evaporation of the solvent gave an oil which was purified by chromatography using ethyl acetate and then 10% methanol / ethyl acetate as eluent to give title compound as a

15 solid (1.8 g, 70%); NMR spectrum (DMSO-d₆) 2.5 (s, 3H), 6.7 - 6.9 (t, 1H), 7.2 (t, 1H), 7.6 (s, 1H), 7.95 - 8.05 (dd, 1H), 8.15 - 8.25 (dd, 1H); Mass spectrum MH^+ 254.

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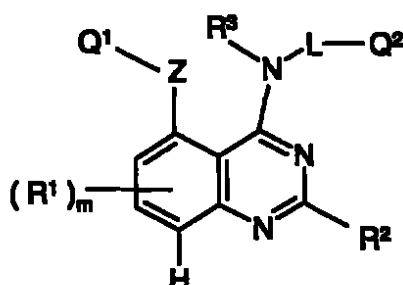
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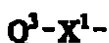
1. A quinazoline derivative of the Formula I



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wherein m is 0, 1 or 2;

- each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- wherein X¹ is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein each R⁴ is, independently, hydrogen or (1-6C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_m is (1-3C)alkylenedioxy,

- and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C=C wherein R⁵ is hydrogen or (1-6C)alkyl,

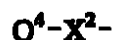
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and wherein any $\text{CH}_2=\text{CH}-$ or $\text{HC}\equiv\text{C}-$ group within a R^1 substituent optionally bears at the terminal $\text{CH}_2=$ or $\text{HC}\equiv$ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$, $\text{N,N-di-}[(1-6\text{C})\text{alkyl}]\text{carbamoyl}$, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or

5 from a group of the formula :



wherein X^2 is a direct bond or is selected from CO and $\text{N}(\text{R}^6)\text{CO}$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

10 and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$, $\text{N,N-di-}[(1-6\text{C})\text{alkyl}]\text{carbamoyl}$,

15 (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, $\text{N}-(1-6\text{C})\text{alkyl-(2-6C)alkanoylamino}$, $\text{N}-(1-6\text{C})\text{alkylsulphamoyl}$, $\text{N,N-di-}[(1-6\text{C})\text{alkyl}]\text{sulphamoyl}$, (1-6C)alkanesulphonylamino and $\text{N}-(1-6\text{C})\text{alkyl-(1-6C)alkanesulphonylamino}$, or from a group of the formula :

20 $-\text{X}^3-\text{Q}^5$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2 , $\text{N}(\text{R}^7)$, CO, $\text{CH}(\text{OR}^7)$, $\text{CON}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{CO}$, $\text{SO}_2\text{N}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{SO}_2$, $\text{C}(\text{R}^7)_2\text{O}$, $\text{C}(\text{R}^7)_2\text{S}$ and $\text{N}(\text{R}^7)\text{C}(\text{R}^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl,

25 heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenylloxy,

30 (2-6C)alkynylloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$, $\text{N,N-di-}[(1-6\text{C})\text{alkyl}]\text{carbamoyl}$, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,

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N-(1-6C)alkyl-(2-6C)alkanoylamino, amino(2-6C)alkanoyl,
 N-(1-6C)alkylamino(2-6C)alkanoyl, N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl,
 N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino,
 and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula:

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wherein X^4 is a direct bond or is selected from O and N(R^8), wherein R^8 is hydrogen or
 (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, carboxy-(1-6C)alkyl,
 (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,
 (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,

10 (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
 carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl,
 N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or
 (1-6C)alkoxycarbonyl-(1-6C)alkyl, or from a group of the formula :



15 wherein X^5 is a direct bond or is selected from O, CO and N(R^{10}), wherein R^{10} is hydrogen or
 (1-6C)alkyl, and Q^6 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl
 or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the
 same or different, selected from halogeno, hydroxy, amino, (1-6C)alkyl, (1-6C)alkoxy,
 (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

20 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2
 oxo or thioxo substituents;

R^2 is hydrogen;

R^3 is hydrogen or (1-6C)alkyl;

Z is a direct bond or is selected from O, S, SO, SO₂, N(R^{11}), CO, CH(OR¹¹),

25 CON(R^{11}), N(R^{11})CO, SO₂N(R^{11}), N(R^{11})SO₂, OC(R^{11})₂, SC(R^{11})₂ and N(R^{11})C(R^{11})₂,
 wherein each R^{11} is, independently, hydrogen or (1-6C)alkyl;

Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl,
 (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl,
 heterocyclyl or heterocyclyl-(1-6C)alkyl,

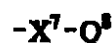
30 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q^1 -Z-
 group are optionally separated by the insertion into the chain of a group selected from O, S,

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SO, SO₂, N(R¹²), CO, CH(OR¹²), CON(R¹²), N(R¹²)CO, SO₂N(R¹²), N(R¹²)SO₂, CH=CH and C≡C wherein R¹² is hydrogen or (1-6C)alkyl,

- and wherein any CH₂ or CH₃ group within the Q¹-Z- group optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent
- 5 selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl,
- 10 N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- wherein X⁷ is a direct bond or is selected from O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S and N(R¹⁴)C(R¹⁴)₂,
- 15 wherein R¹⁴ is hydrogen or (1-6C)alkyl, and Q⁸ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- and wherein any aryl, heteroaryl or heterocyclyl group within the Q¹-Z- group
- 20 optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,
- 25 N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, amino(2-6C)alkanoyl, N-(1-6C)alkylamino(2-6C)alkanoyl, N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

- 30 $-X^8-R^{15}$

wherein X⁸ is a direct bond or is selected from O and N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and R¹⁵ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl,

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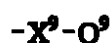
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(1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl,

di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,

N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl,

- 5 (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl, or from a group of the formula:

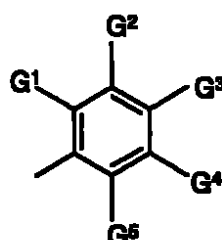


wherein X^9 is a direct bond or is selected from O, CO and $N(R^{17})$, wherein R^{17} is hydrogen or (1-6C)alkyl, and Q^9 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl

- 10 or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1 or 2 oxo or thioxo substituents;

Q^2 is an aryl group of formula Ia



Ia

15

wherein G^1 and G^5 are hydrogen,

G^2 and G^4 each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino,

- 20 di-[(1-6C)alkyl]amino, aryl and heteroaryl,

and wherein an aryl or heteroaryl group within any of G^2 and G^4 optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl,

- 25 (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

G^3 is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl,

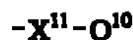
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(1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, 5 N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^{10} is a direct bond or is selected from O and $N(R^{19})$, wherein R^{19} is hydrogen or 10 (1-6C)alkyl, and R^{18} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



15 wherein X^{11} is a direct bond or is selected from O, S, SO, SO₂, $N(R^{20})$, CO, CH(OR²⁰), CON(R²⁰), $N(R^{20})$ CO, SO₂N(R²⁰), $N(R^{20})$ SO₂, C(R²⁰)₂O, C(R²⁰)₂S, C(R²⁰)₂N(R²⁰) and $N(R^{20})$ C(R²⁰)₂, wherein R^{20} is hydrogen or (1-6C)alkyl, and Q^{10} is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or 20 heterocyclyl-(1-6C)alkyl,

and wherein Q^{10} optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, formyl, carbamoyl, sulphamoyl, mercapto, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, 25 (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

30 $-X^{13}-R^{23}$

wherein X^{13} is a direct bond or is selected from O and $N(R^{24})$, wherein R^{24} is hydrogen or (1-6C)alkyl, and R^{23} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl,

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- (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, 5 (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl, and wherein any heterocyclyl group within Q¹⁰ optionally bears 1 or 2 oxo or thioxo substituents, or G³ and G⁴ together form a group of formula :- -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-, 10 -CH=N-CH=N-, -N=CH-CH=N-, -N=N-CH=CH-, -CH=CH-N=N-, -CH=CH-O-, -O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH₂-CH₂-O-, -O-CH₂-CH₂-, -CH₂-CH₂-S-, -S-CH₂-CH₂-, -O-CH₂-O-, -O-CH₂-CH₂-O-, -S-CH₂-S-, -S-CH₂-CH₂-S-, -CH=CH-NH-, -NH-CH=CH-, -CH₂-CH₂-NH-, -NH-CH₂-CH₂-, -N=CH-NH-, -NH-CH=N-, -NH-CH₂-NH-, -O-CH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH₂-NH-, -NH-CH₂-O-, 15 -S-CH₂-NH-, -NH-CH₂-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -CH=N-S-, -O-NH-CH₂-, -CH₂-NH-O-, -S-NH-CH₂-, -CH₂-NH-S-, -NH-N=CH-, -CH=N-NH-, -NH-NH-CH₂-, -CH₂-NH-NH-, -N=N-NH- or -NH-N=N-,

- and the 9- or 10-membered bicyclic heteroaryl or heterocyclic ring formed when G³ and G⁴ together are linked optionally bears on the heteroaryl or heterocyclic portion of the 20 bicyclic ring 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino and a group of the formula:



- 25 wherein X¹² is a direct bond or is selected from O, SO, SO₂, N(R²¹), SO₂N(R²¹) and CO, wherein R²¹ is hydrogen or (1-6C)alkyl and Q¹¹ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, formyl, carbamoyl, sulphamoyl, mercapto, 30 (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,

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N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

5 $-X^{14}-R^{25}$

wherein X^{14} is a direct bond or is selected from O and $N(R^{26})$, wherein R^{26} is hydrogen or (1-6C)alkyl, and R^{25} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl,

10 di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl; and

L is a direct bond or $-[C(R^{22})_2]_n-$, wherein n is 1 or 2, and each R^{22} independently is hydrogen or (1-4C)alkyl,

15 and when L is a direct bond at least one of G^2 , G^3 and G^4 is other than H; or a pharmaceutically-acceptable salt thereof.

2. A quinazoline derivative according to claim 1, or a pharmaceutically acceptable salt thereof, wherein m is as defined in claim 1 and

20 each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, 25 N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

30 Q^3-X^1-

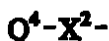
wherein X^1 is a direct bond or is selected from O, S, SO, SO₂, $N(R^4)$, CO, CH(OR⁴), CON(R⁴), $N(R^4)CO$, SO₂ $N(R^4)$, $N(R^4)SO_2$, OC(R⁴)₂, SC(R⁴)₂ and $N(R^4)C(R^4)_2$, wherein each

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R^4 is, independently, hydrogen or (1-6C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_m$ is (1-3C)alkylenedioxy,

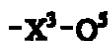
- 5 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2 , $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, $CH=CH$ and $C=C$ wherein R^5 is hydrogen or (1-6C)alkyl,

- and wherein any $CH_2=CH-$ or $HC=C-$ group within a R^1 substituent optionally bears at
10 the terminal $CH_2=$ or $HC=$ position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



- 15 wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent
20 selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N -(1-6C)alkyl-(2-6C)alkanoylamino, N -(1-6C)alkylsulphamoyl, N,N -di-[(1-6C)alkyl]sulphamoyl,
25 (1-6C)alkanesulphonylamino and N -(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- wherein X^3 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^7)$, CO, $CH(OR^7)$,
30 $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl,

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(3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

- and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from
- 5 halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, 10 N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



- wherein X⁴ is a direct bond or is selected from O and N(R⁹), wherein R⁹ is hydrogen or
- 15 (1-6C)alkyl, and R⁸ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula:

- 20 $-X^4-Q^6$

wherein X⁴ is a direct bond or is selected from O, CO and N(R¹⁰), wherein R¹⁰ is hydrogen or (1-6C)alkyl, and Q⁶ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

- 25 and wherein any heterocyclyl group within a substituent on R¹ optionally bears 1 or 2 oxo or thioxo substituents;

R² is hydrogen;

R³ is hydrogen or (1-6C)alkyl;

Z is a direct bond or is selected from O, S, SO, SO₂, N(R¹¹), CO, CH(OR¹¹),

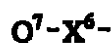
- 30 CON(R¹¹), N(R¹¹)CO, SO₂N(R¹¹), N(R¹¹)SO₂, OC(R¹¹)₂, SC(R¹¹)₂ and N(R¹¹)C(R¹¹)₂, wherein each R¹¹ is, independently, hydrogen or (1-6C)alkyl;

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Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

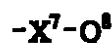
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q^1 -Z- group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹²), CO, CH(OR¹²), CON(R¹²), N(R¹²)CO, SO₂N(R¹²), N(R¹²)SO₂, CH=CH and C=C wherein R¹² is hydrogen or (1-6C)alkyl,

and wherein any CH₂=CH- or HC=C- group within the Q^1 -Z- group optionally bears at the terminal CH₂= or HC= position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



wherein X⁶ is a direct bond or is selected from CO and N(R¹³)CO, wherein R¹³ is hydrogen or (1-6C)alkyl, and Q⁷ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH₂ or CH₃ group within the Q^1 -Z- group optionally bears on each said CH₂ or CH₃ group one or more halogeno or (1-6C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphiny, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X⁷ is a direct bond or is selected from O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S and N(R¹⁴)C(R¹⁴)₂,

wherein R¹⁴ is hydrogen or (1-6C)alkyl, and Q⁸ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

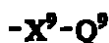
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- and wherein any aryl, heteroaryl or heterocyclyl group within the Q¹-Z- group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, 5 (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and 10 N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



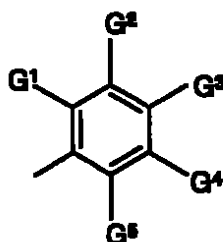
- wherein X⁸ is a direct bond or is selected from O and N(R¹⁶), wherein R¹⁶ is hydrogen or (1-6C)alkyl, and R¹⁵ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, 15 (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula:



- wherein X⁹ is a direct bond or is selected from O, CO and N(R¹⁷), wherein R¹⁷ is hydrogen or (1-6C)alkyl, and Q⁹ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl 20 or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo or thioxo substituents;

Q² is an aryl group of formula Ia



Ia

25

wherein G¹ and G⁵ are hydrogen,

G² and G⁴ each independently is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl,

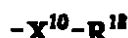
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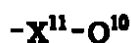
(1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, aryl and heteroaryl,

and wherein an aryl or heteroaryl group within any of G² and G⁴ optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

G³ is selected from hydrogen, halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N-(1-6C)alkyl-(3-6C)alkynoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X¹⁰ is a direct bond or is selected from O and N(R¹⁹), wherein R¹⁹ is hydrogen or (1-6C)alkyl, and R¹⁸ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X¹¹ is a direct bond or is selected from O, S, SO, SO₂, N(R²⁰), CO, CH(OR²⁰), CON(R²⁰), N(R²⁰)CO, SO₂N(R²⁰), N(R²⁰)SO₂, C(R²⁰)₂O, C(R²⁰)₂S and N(R²⁰)C(R²⁰)₂, wherein R²⁰ is hydrogen or (1-6C)alkyl, and Q¹⁰ is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein Q¹⁰ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy,

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- (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, 5 N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein any heterocyclyl group within Q^{10} optionally bears 1 or 2 oxo or thioxo substituents,

or G^3 and G^4 together form a group of formula :- $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$,

- 10 $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$, $-\text{N}=\text{CH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-\text{CH}=\text{N}-$, $-\text{N}=\text{CH}-\text{CH}=\text{N}-$, $-\text{N}=\text{N}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{N}=\text{N}-$, $-\text{CH}=\text{CH}-\text{O}-$, $-\text{O}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{S}-$, $-\text{S}-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}_2-\text{O}-$, $-\text{O}-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{S}-$, $-\text{S}-\text{CH}_2-\text{CH}_2-$, $-\text{O}-\text{CH}_2-\text{O}-$, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$, $-\text{S}-\text{CH}_2-\text{S}-$, $-\text{S}-\text{CH}_2-\text{CH}_2-\text{S}-$, $-\text{CH}=\text{CH}-\text{NH}-$, $-\text{NH}-\text{CH}=\text{CH}-$, $-\text{CH}_2-\text{CH}_2-\text{NH}-$, $-\text{NH}-\text{CH}_2-\text{CH}_2-$, $-\text{N}=\text{CH}-\text{NH}-$, $-\text{NH}-\text{CH}=\text{N}-$, $-\text{NH}-\text{CH}_2-\text{NH}-$, 15 $-\text{O}-\text{CH}=\text{N}-$, $-\text{N}=\text{CH}-\text{O}-$, $-\text{S}-\text{CH}=\text{N}-$, $-\text{N}=\text{CH}-\text{S}-$, $-\text{O}-\text{CH}_2-\text{NH}-$, $-\text{NH}-\text{CH}_2-\text{O}-$, $-\text{S}-\text{CH}_2-\text{NH}-$, $-\text{NH}-\text{CH}_2-\text{S}-$, $-\text{O}-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-\text{O}-$, $-\text{S}-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-\text{S}-$, $-\text{O}-\text{NH}-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-\text{O}-$, $-\text{S}-\text{NH}-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-\text{S}-$, $-\text{NH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-\text{NH}-$, $-\text{NH}-\text{NH}-\text{CH}_2-$, $-\text{CH}_2-\text{NH}-\text{NH}-$, $-\text{N}=\text{N}-\text{NH}-$ or $-\text{NH}-\text{N}=\text{N}-$,

- and the 9- or 10-membered bicyclic heteroaryl or heterocyclic ring formed when G^3 20 and G^4 together are linked optionally bears on the heteroaryl or heterocyclic portion of the bicyclic ring 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula:

- 25 $-\text{X}^{12}-\text{Q}^{11}$

- wherein X^{12} is a direct bond or is selected from O, SO, SO₂, N(R²¹) and CO, wherein R²¹ is hydrogen or (1-6C)alkyl and Q¹¹ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy, and any 30 bicyclic heterocyclic ring so formed optionally bears 1 or 2 oxo or thioxo groups; and

L is a direct bond or $-\text{C}(\text{R}^{22})_n-$, wherein n is 1 or 2, and each R²² independently is hydrogen or (1-4C)alkyl,

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and when L is a direct bond at least one of G^2 , G^3 and G^4 is other than H;
or a pharmaceutically-acceptable salt thereof.

3. A quinazoline derivative according to claim 1, or a pharmaceutically acceptable salt
5 thereof, wherein each of m, R^1 , R^2 , R^3 , L and Q^2 is as defined in claim 1 and

Z is selected from O, S, SO, SO_2 , $N(R^{11})$, CO, $CH(OR^{11})$, $CON(R^{11})$, $N(R^{11})CO$,
 $SO_2N(R^{11})$, $N(R^{11})SO_2$, $OC(R^{11})_2$, $SC(R^{11})_2$ and $N(R^{11})C(R^{11})_2$, wherein R^{11} is hydrogen or
(1-6C)alkyl; and

Q^1 is selected from (3-7C)cycloalkyl, (3-7C)cycloalkenyl and heterocyclyl,
10 and wherein any CH_2 or CH_3 group within the Q^1 -Z- group optionally bears on each
said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents or a substituent
selected from hydroxy, cyano, amino, carboxy, carbamoyl, (1-6C)alkoxy, (1-6C)alkylthio,
(1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,
di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl,
15 N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
 N -(1-6C)alkyl-(2-6C)alkanoylamino, N -(1-6C)alkylsulphamoyl,
 N,N -di-[(1-6C)alkyl]sulphamoyl,
(1-6C)alkanesulphonylamino and N -(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a
group of the formula :

20 $-X^7-Q^8$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^{14})$, CO, $CH(OR^{14})$,
 $CON(R^{14})$, $N(R^{14})CO$, $SO_2N(R^{14})$, $N(R^{14})SO_2$, $C(R^{14})_2O$, $C(R^{14})_2S$ and $N(R^{14})C(R^{14})_2$,
wherein R^{14} is hydrogen or (1-6C)alkyl, and Q^8 is (3-7C)cycloalkyl,
(3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl,

25 heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1, 2 or 3
substituents, which may be the same or different, selected from halogeno, trifluoromethyl,
cyano, nitro, hydroxy, amino, carboxy, carbamoyl, formyl, (1-6C)alkyl, (2-8C)alkenyl,
(2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio,
30 (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,
(1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl,
(2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,

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N-(1-6C)alkyl-(2-6C)alkanoylamino, amino(2-6C)alkanoyl,
N-(1-6C)alkylamino(2-6C)alkanoyl, N,N-di-[(1-6C)alkyl]amino(2-6C)alkanoyl,
N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino
 and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

5 $-X^8-R^{15}$

wherein X^8 is a direct bond or is selected from O and N(R^{16}), wherein R^{16} is hydrogen or
 (1-6C)alkyl, and R^{15} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl,
 (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl,
 (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,
 10 N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl,
 (2-6C)alkanoyl-(1-6C)alkyl or (1-6C)alkoxycarbonyl-(1-6C)alkyl, or from a group of the
 formula:

$-X^9-Q^9$

wherein X^9 is a direct bond or is selected from O, CO and N(R^{17}), wherein R^{17} is hydrogen or
 15 (1-6C)alkyl, and Q^9 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2
 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl and
 (1-6C)alkoxy,
 and wherein any heterocyclyl group within the Q^1 -Z- group optionally bears 1 or 2 oxo or
 thioxo substituents.

20

4. A quinoxaline derivative according to claim 1, or a pharmaceutically acceptable salt
 thereof, wherein each of R^2 , R^3 , L, Z, Q^1 and Q^2 is as defined in claim 1 and

m is 1; and

the R^1 group is located at the 7-position and is a group of the formula :

25 Q^3-X^1-

wherein X^1 is O and Q^3 is selected from heterocyclyl-propyl or heterocyclyl-butyl, wherein
 said heterocyclyl group contains at least 1 nitrogen atom,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1
 substituent are optionally separated by the insertion into the chain of a group selected from O,

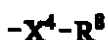
30 S, N(R^5), CO, CH=CH and C=C wherein R^5 is hydrogen or (1-6C)alkyl,

and wherein any heterocyclyl group within R^1 optionally bears 1 or 2 substituents,
 which may be the same or different, selected from halogeno, hydroxy, carbamoyl, (1-

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4C)alkyl, (1-4C)alkoxy, (2-4C)alkenyl, (2-4C)alkynyl, (2-4C)alkanoyl, (1-4C)alkylsulphonyl, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl and N,N-di-[(1-4C)alkyl]carbamoyl, or optionally bears 1 substituent selected from a group of the formula :



- 5 wherein X^4 is a direct bond or is selected from O and NH, and R^8 is 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, fluoromethyl, 2-fluoroethyl, chloromethyl, 2-chloroethyl, acetylmethyl, acetamidomethyl, carbamoylmethyl, 2-carbamoylethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, 10 cyanomethyl, cyanoethyl, methoxycarbonylaminomethyl or ethoxycarbonylaminomethyl, and wherein any heterocyclyl group within R^1 optionally bears 1 oxo substituent.

5. A quinazoline derivative according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein each of R^2 , R^3 , L, Z, Q^1 and Q^2 is as defined in claim 1 or 15 claim 2, and

m is 1; and

- the R^1 group is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, pyrrolidin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 20 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy, 3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy, and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R^1 substituent 25 are optionally separated by the insertion into the chain of a group selected from O, NH and $N(CH_3)$,

- and wherein any terminal CH_3 group within a (1-6C)alkoxy chain in a R^1 substituent optionally bears on the terminal CH_3 group a substituent selected from hydroxy, amino and N -(1-methylpyrrolidin-3-yl)- N -methylamino, 30 and wherein any pyrrolidinyl or piperidinyl group within a R^1 substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,

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and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl, 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl.

5 6. A quinazoline derivative according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each of R^2 , R^3 , L, Z, Q^1 and Q^2 is as defined in claim 1 and

m is 1; and

the R^1 group is located at the 7-position and is (1-3C)alkoxy or (1-3C)alkoxy(1-3C)alkoxy.

10

7. A quinazoline derivative according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^3 , m, L and Q^2 is as defined in claim 1 and

Z is O; and

the Q^1 -Z- group is selected from pyrrolidin-3-yl, piperidin-3-yl and

15 piperidin-4-yl, and

wherein any NH group within a pyrrolidinyl or piperidinyl group in Q^1 optionally bears a substituent selected from methyl, ethyl, allyl, acetyl, carbamoyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, 2-fluoroethyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, acetylmethyl

20 and methoxycarbonylmethyl,

and

wherein any pyrrolidinyl or piperidinyl group within the Q^1 -Z- group optionally bears 1 oxo substituent.

25 8. A quinazoline derivative according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^3 , m, L and Q^2 is as defined in claim 1 and

Z is O; and

Q^1 is selected from tetrahydrofuran-3-yl, tetrahydropyran-3-yl and tetrahydropyran-4-yl,

30 and wherein any tetrahydrofuranyl or tetrahydropyranyl group within Q^1 optionally bears 1 or 2 substituents selected from fluoro, chloro, hydroxy, methyl, ethyl and amino, and

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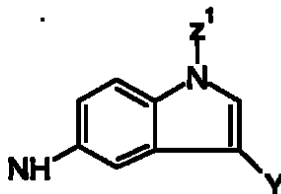
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wherein any tetrahydrofuranyl or tetrahydropyranyl group within the Q^1 -Z- group optionally bears 1 oxo substituent.

9. A quinazoline derivative according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , m, Z and Q^1 is as defined in claim 1 and

the group $Q^2LN(R^3)$ is selected from 3-chloro-4-fluoroanilino, 3-chloro-4-hydroxyanilino, 3-fluoroanilino, 3-bromoanilino, 3-chloroanilino, 3-methylanilino and 3-ethynylanilino.

10. A quinazoline derivative according to claim 1, or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , m, Z and Q^1 is as defined in claim 1 and the group $Q^2LN(R^3)$ is a group of the formula Ic:



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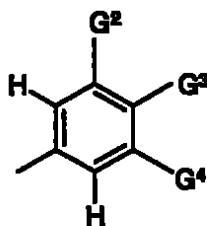
Ic

wherein Z^1 is hydrogen or (1-4C)alkyl, and

Y is selected from hydrogen, halogeno, (1-4C)alkyl and cyano.

11. A quinazoline derivative according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^3 , m, L, Z and Q^1 is as defined in claim 1 or claim 2, and

Q^2 is an aryl group of formula Ib:



Ib

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wherein G^3 and G^4 together form a group of formula: -NH-CH=CH- or -NH-N=CH-,
 and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 are linked
 together optionally bears on a NH group of the heteroaryl portion of the bicyclic ring a group
 of the formula:

5 $-X^{12}-Q^{11}$

wherein X^{12} is a direct bond or is SO_2 and Q^{11} is benzyl or 2-pyridylmethyl, which optionally
 bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro,
 bromo, cyano, hydroxy and methyl,

and the 9-membered bicyclic heteroaryl ring formed when G^3 and G^4 together are
 10 linked optionally bears at the 3-position in the heteroaryl portion of the bicyclic ring 1:
 substituent selected from fluoro, chloro, bromo, cyano, hydroxy, amino, methyl, ethyl and
 ethynyl,

and G^2 is selected from hydrogen, fluoro, chloro, bromo, cyano, hydroxy, amino,
 methyl, ethyl and ethynyl.

15

12. A quinazoline derivative according to claim 1, or a pharmaceutically acceptable salt
 thereof, wherein each of R^2 , R^3 , Z, L and Q^1 is as defined in claim 1 and

Q^2 is a group of formula Ia as defined in claim 1 wherein:

G^1 , G^2 and G^3 are hydrogen,

20 G^4 is selected from hydrogen, halogeno, (1-6C)alkyl and (2-6C)alkynyl, and

G^5 is a group of the formula:

$-X^{11}-Q^{10}$

wherein X^{11} is O and Q^{10} is selected from benzyl and heteroaryl-methyl, and wherein any
 phenyl or heteroaryl group within Q^{10} optionally bears 1 or 2 substituents, which may be the
 25 same or different, selected from selected from halogeno, hydroxy, cyano, amino, (1-6C)alkyl,
 (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, carbamoyl,
N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, halogeno-(1-6C)alkyl,
 hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl,
 (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl,
 30 N-(1-6C)alkylcarbamoyl-(1-6C)alkyl and N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl;

m is 1; and

R^1 is located at the 7-position and is as defined in claim 1.



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13. A quinoxaline derivative of the formula I as defined in claim 1 wherein:
 m is 0 or 1 and the R¹ group, when present, is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy,
 5 pyrrolidin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy, 3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and
 10 3-homopiperazin-1-ylpropoxy,
 and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH and N(CH₃),
 and wherein any terminal CH₃ group within a (1-6C)alkoxy chain in a R¹ substituent
 15 optionally bears on said terminal CH₃ group a substituent selected from hydroxy, amino and N-(1-methylpyrrolidin-3-yl)-N-methylamino,
 and wherein any pyrrolidinyl or piperidinyl group within a R¹ substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,
 and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent
 20 optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl, 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl;
 the Q¹-Z- group is selected from cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy,
 25 1,1-dioxodotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy and azetidin-3-yloxy,
 and wherein the azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within the Q¹-Z- group is optionally N- substituted by a substituent selected from methyl, ethyl,
 30 n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, allyl, 2-propynyl, acetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl,

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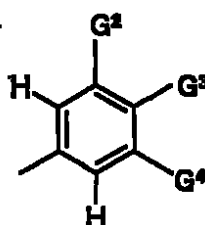
N,N-dimethylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, acetylmethyl, 2-acetylethyl, methoxycarbonylmethyl and 2-methoxycarbonylethyl,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2
5 oxo substituents;

R² and R³ are hydrogen;

L is a direct bond; and

Q² is an aryl group of formula Ib



10

Ib

wherein G² is hydrogen, and G³ and G⁴, which may be the same or different, is selected from hydrogen, fluoro, chloro, bromo, cyano, hydroxy, methyl, ethyl, and ethynyl, provided that at least one of G³ and G⁴ is other than hydrogen,

15 or G³ and G⁴ together form a group of formula :-CH=CH-NH-, -NH-CH=CH-, -NH-N=CH-, -CH=N-NH-, and the 9-membered bicyclic heteroaryl ring so formed optionally bears on the heteroaryl portion of the bicyclic ring 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano, and methyl;
or a pharmaceutically-acceptable acid-addition salt thereof.

20

14. A quinazoline derivative of the formula I as defined in claim 1 wherein:

m is 1 and the R¹ group is located at the 7-position and is selected from hydroxy, amino, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, pyrrolidin-1-yl,

2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy,

25 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy,

3-piperidin-4-ylpropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,

2-morpholinoethoxy, 3-morpholinopropoxy, 2-homopiperidinoethoxy,

3-homopiperidinopropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy

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and wherein adjacent carbon atoms in any (2-6C)alkoxy chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, NH and N(CH₃),

and wherein any terminal CH₃ group within a (1-6C)alkoxy chain in a R¹ substituent
5 optionally bears on the terminal CH₃ group a substituent selected from hydroxy, amino and N-(1-methylpyrrolidin-3-yl)-N-methylamino,

and wherein any pyrrolidinyl or piperidinyl group within a R¹ substituent optionally bears a substituent selected from hydroxy, methyl, amino, methylamino and dimethylamino,

and wherein any piperazin-1-yl or homopiperazin-1-yl group within a R¹ substituent
10 optionally bears a substituent at the 4-position selected from methyl, ethyl, isopropyl, 2-methoxyethyl, tetrahydrofurfuryl, 2-morpholinoethyl and 1-methylpiperidin-4-yl;

the Q¹-Z- group is selected from cyclopentyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothiopyran-4-yloxy, 1,1-dioxotetrahydrothiopyran-4-yloxy, 1-oxotetrahydrothiopyran-4-yloxy, tetrahydrothien-3-yloxy,

15 1,1-dioxodotetrahydrothien-3-yloxy, 1-oxotetrahydrothien-3-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-yloxy, piperidin-3-yloxy, piperidin-4-yloxy, homopiperidin-3-yloxy, homopiperidin-4-yloxy and azetidin-3-yloxy,

and wherein the azetidiny, pyrrolidinyl, piperidinyl or homopiperidinyl group within the Q¹-Z- group is optionally N- substituted by a substituent selected from methyl, ethyl,

20 n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, allyl, 2-propynyl, acetyl, propionyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, 2-methoxyethyl, carbamoylmethyl, N-methylcarbamoylmethyl, N,N-di-methylcarbamoylmethyl, 2-carbamoylethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N,N-di-methylcarbamoyl)ethyl, acetylmethyl, 2-acetylethyl, methoxycarbonylmethyl and
25 2-methoxycarbonylethyl,

and wherein any heterocyclyl group within the Q¹-Z- group optionally bears 1 or 2 oxo substituents;

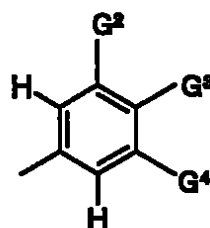
R² and R³ are hydrogen;

L is a direct bond; and

30 Q² is an aryl group of formula Ib

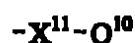
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1b

wherein G^3 is a group of the formula:



- 5 wherein X^{11} is a direct bond or is selected from O, S, $N(R^{20})$, CO, $CH(OR^{20})$ and $C(R^{20})_2NR^{20}$, wherein R^{20} is hydrogen or methyl, and Q^{10} is a phenyl or benzyl group which is optionally substituted with 1 or 2 substituents selected from fluoro, chloro, bromo, trifluoromethyl, nitro, methyl, ethyl, isopropyl, ethynyl and cyano, or Q^{10} is a heteroaryl moiety selected from 2-1H-imidazolyl, 2-1H-imidazolylmethyl,
- 10 4-thiazolylmethyl, 2-thienylmethyl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-3-ylmethyl, 3-isoxazolylmethyl, 2-, 3- or 4-pyridyl, 2-, 3- or 4-pyridylmethyl, 8-quinoliny, and 8-quinolinylmethyl, which heteroaryl moiety is optionally substituted with one or two substituents selected from fluoro, chloro, bromo, trifluoromethyl, methyl, ethynyl and cyano, and each of G^2 and G^4 independently is selected from hydrogen, fluoro, chloro, bromo,
- 15 methyl, and ethynyl;
or a pharmaceutically acceptable salt thereof.
15. A quinazoline derivative of the formula I as defined in claim 1 wherein:
m is 1 and the R^1 group is located at the 7 position and is selected from
- 20 3-pyrrolidin-1-ylpropoxy, 3-pyrrolidin-2-ylpropoxy, 3-pyrrolidin-3-ylpropoxy, 3-morpholinopropoxy, 3-piperidinopropoxy, 3-piperidin-2-ylpropoxy, 3-piperidin-3-ylpropoxy, 3-piperidin-4-ylpropoxy and 3-piperazin-1-ylpropoxy,
and wherein any heterocyclyl group within a R^1 substituent optionally bears a substituent selected from hydroxy, carbamoyl, methyl, ethyl, allyl, acetyl, N-methylcarbamoyl
- 25 N,N-dimethylcarbamoyl, 2-methoxyethyl, carbamoylmethyl, N,N-dimethylcarbamoylmethyl, acetylmethyl and cyanomethyl,
and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 oxo substituent;

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Z is O;

Q¹ is tetrahydrofuran-3-yl, tetrahydropyran-4-yl or tetrahydropyran-3-yl,

R² is hydrogen; and

Q²LN(R³) is selected from 3-chloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-chloroanilino, 3-methylanilino and 3-ethynylanilino; or a pharmaceutically acceptable salt thereof.

16. A quinazoline derivative of the formula I as defined in claim 1 wherein:

m is 0 or 1 and the **R¹** group, when present is located at the 7 position and is selected from (1-3C)alkoxy and (1-3C)alkoxy(1-3C)alkoxy;

10 **Z** is O;

Q¹ is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl, and wherein any NH group within a pyrrolidinyl or piperidinyl group in **Q¹** optionally bears a substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, or from a group of the

15 formula:



wherein **X⁸** is a direct bond and **R¹⁵** is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methylcarbamoyl-(1-3C)alkyl,

N,N-dimethylcarbamoyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or

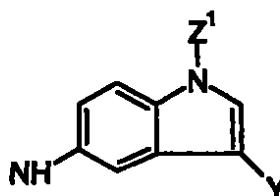
20 methoxycarbonyl-(1-3C)alkyl,

and wherein any pyrrolidinyl or piperidinyl group within the **Q¹-Z-** group optionally bears 1 oxo substituent;

R² is hydrogen; and

Q²LN(R³) is a group of the formula Ic:

25



Ic

wherein **Z¹** is hydrogen or (1-4C)alkyl, and



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Y is selected from hydrogen, halogeno, (1-4C)alkyl and cyano;
or a pharmaceutically acceptable salt thereof.

17. A quinazoline derivative of the formula I as defined in claim 1 wherein:

5 m is 1 and the R¹ group is located at the 7 position and is selected from (1-3C)alkoxy and (1-3C)alkoxy(1-3C)alkoxy;

Z is O;

Q¹ is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl, and
wherein any NH group within a pyrrolidinyl or piperidinyl group in Q¹ optionally bears a
10 substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl,
ethoxycarbonyl, N-methylcarbamoyl and N,N-dimethylcarbamoyl, or from a group of the
formula:



wherein X⁸ is a direct bond, and R¹⁵ is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-
15 (1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methylcarbamoyl-(1-3C)alkyl,
N,N-dimethylcarbamoyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or methoxycarbonyl-(1-3C)alkyl,
and wherein any pyrrolidinyl or piperidinyl group within the Q¹-Z- group optionally bears 1
oxo substituent;

R² and R³ are hydrogen;

20 L is a direct bond; and

Q² is a group of formula Ia as defined in claim 1 wherein:

G¹, G² and G³ are hydrogen, and

G³ and G⁴ together form a group of the formula: -NH-CH=CH-, and the indolyl ring
so formed by G³ and G⁴ together with the carbon atoms to which they are attached is

25 substituted at the 1-position by a group of the formula:



wherein X¹² is a direct bond and Q¹¹ is benzyl which is optionally substituted by 1 or 2
substituents, which may be the same or different, selected from fluoro, chloro, bromo, cyano,
methyl and ethyl, and

30 wherein the indolyl ring so formed by G³ and G⁴ together with the carbon atoms to which
they are attached is optionally substituted at the 3-position by a substituent selected from
chloro and bromo;

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or a pharmaceutically acceptable salt thereof.

18. A quinazoline derivative of the formula I as defined in claim 1 wherein:

m is 1 and the R¹ group is located at the 7 position and is selected from (1-3C)alkoxy,

5 (1-3C)alkoxy(1-3C)alkoxy and piperidin-4-ylmethoxy;

Z is O;

Q¹ is selected from pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl and tetrahydropyran-4-yl, and

wherein any NH group within a pyrrolidinyl or piperidinyl group in Q¹ optionally bears a
10 substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, or from a group of the formula:



wherein X⁸ is a direct bond, and R¹⁵ is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-
15 (1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methylcarbamoyl-(1-3C)alkyl, N,N-di-methylcarbamoyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or methoxycarbonyl-(1-3C)alkyl, and wherein any pyrrolidinyl or piperidinyl group within the Q¹-Z- group optionally bears 1 oxo substituent;

R² and R³ are hydrogen;

20 L is a direct bond; and

Q² is a group of formula Ia as defined in claim 1 wherein:

G¹, G² and G³ are hydrogen,

G⁴ is selected from chloro, methyl and ethynyl, and

G³ is a group of the formula:

25 $-X^{11}-Q^{10}$

wherein X¹¹ is O and Q¹⁰ is benzyl which is optionally substituted by 1 or 2 substituents, which may be the same or different, selected from fluoro, cyano and methyl;
or a pharmaceutically acceptable salt thereof.

30 19. A quinazoline derivative of the formula I as defined in claim 1 wherein:

m is 1 and the R¹ group is located at the 7 position and is selected from (1-3C)alkoxy and (1-3C)alkoxy(1-3C)alkoxy;



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Z is O;

Q¹ is selected from pyrrolidin-3-yl, piperidin-3-yl and piperidin-4-yl, and wherein any NH group within a pyrrolidinyl or piperidinyl group in Q¹ optionally bears a substituent selected from (1-3C)alkyl, allyl, acetyl, carbamoyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, or from a group of the formula:



wherein X⁸ is a direct bond, and R¹⁵ is halogeno-(1-3C)alkyl, methoxy-(1-3C)alkyl, ethoxy-(1-3C)alkyl, carbamoyl-(1-3C)alkyl, N-methylcarbamoyl-(1-3C)alkyl,

- 10 N,N-di-methylcarbamoyl-(1-3C)alkyl, acetyl-(1-3C)alkyl or methoxycarbonyl-(1-3C)alkyl, and wherein any pyrrolidinyl or piperidinyl group within the Q¹-Z- group optionally bears 1 oxo substituent;

R² and R³ are hydrogen;

L is a direct bond; and

- 15 Q² is a group of formula Ia as defined in claim 1 wherein:

G¹, G² and G³ are hydrogen,

G⁴ is selected from chloro and methyl, and

G⁵ is a group of the formula:



- 20 wherein X¹¹ is O and Q¹⁰ is selected from isoxazolylmethyl and thiazolylmethyl, and wherein the heteroaryl group within Q¹⁰ optionally bears a methyl substituent; or a pharmaceutically acceptable salt thereof.

20. A quinazoline derivative of the formula I as defined in claim 1 selected from:

- 25 4-(3-Chloroanilino)-7-(3-(R)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline;
 4-(3-Chloroindol-5-ylamino)-5-(1-methylpiperidin-4-yloxy)quinazoline;
 4-(3-Bromoanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
 4-(3-Chloroindol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
 30 4-(3-Ethynylanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
 4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
 4-(3-Chloroanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;

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- 7-Methoxy-4-(3-methylanilino)-5-(1-methylpiperidin-4-yloxy)quinazoline;
4-(Indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
4-(3-Bromoanilino)-7-(2-methoxyethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline;
4-(3-Chloro-4-fluoroanilino)-7-methoxy-5-(piperidin-4-yloxy)quinazoline;
5 4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(3-(piperidin-1-yl)propoxy)quinazoline;
4-(3-Chloro-4-fluoroanilino)-5-(1-methylpiperidin-4-yloxy)-7-(2-(4-isopropyl-piperazin-1-yl)ethoxy)quinazoline;
4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-hydroxyethyl)-N-methylamino)propoxy]-5-
10 (tetrahydropyran-4-yloxy)quinazoline;
4-(3-Chloro-4-fluoroanilino)-7-[3-(N-(2-dimethylaminoethyl)-N-methylamino)propoxy]-5-
(tetrahydropyran-4-yloxy)quinazoline; and
4-(3-Chloro-4-fluoroanilino)-7-(3-(4-methylpiperazin-1-yl)propoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline;
15 or a pharmaceutically acceptable acid addition salt thereof.
21. A quinazoline derivative of the formula I as defined in claim 1 selected from:
4-(3-Bromoanilino)-7-(3-(*R*)-dimethylaminopyrrolidin-1-yl)-5-(1-methylpiperidin-4-yloxy)quinazoline;
20 4-(3-Bromoindol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
4-(3-Chloro-4-benzyloxyanilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
4-(3-Chloro-4-(3-fluorobenzyloxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
4-(3-Methyl-4-(5-methylisoxazol-3-ylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
25 4-(3-Methyl-4-(thiazol-4-ylmethoxy)anilino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
4-(1-(3-Fluorobenzyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
4-(1-(2-Fluorobenzyl)indol-5-ylamino)-7-methoxy-5-(1-methylpiperidin-4-yloxy)quinazoline;
30 4-(3-Chloro-4-fluoroanilino)-7-(3-morpholinopropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline;
4-(3-Chloro-4-fluoroanilino)-7-(3-pyrrolidin-1-ylpropoxy)-5-(tetrahydrofuran-3-yloxy)quinazoline;

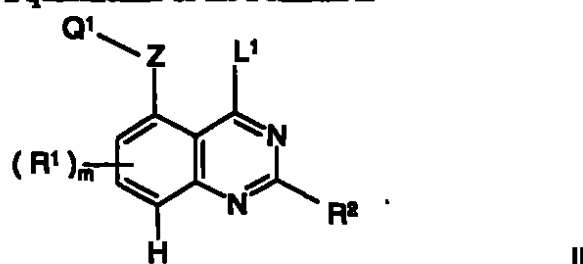
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- 2-[4-(4-(3-Chloro-4-fluoroanilino)-7-methoxyquinazolin-5-yloxy)piperidin-1-yl]acetamide;
 4-(3-Chloro-4-fluoroanilino)-7-(2-methoxyethoxy)-5-(1-methylpiperidin-4-yloxy)quinazoline; and
 4-(3-Chloro-4-fluoroanilino)-7-[3-(4-(N,N-dimethylcarbamoylmethyl)piperazin-1-yl)propoxy]-5-(tetrahydrofuran-3-yloxy)quinazoline;
 or a pharmaceutically acceptable acid addition salt thereof.

22. A process or the preparation of a quinazoline derivative of the formula I, or a salt thereof, according to claim 1 which comprises:

- 10 (a) the reaction of a quinazoline of the Formula II



wherein L¹ is a displaceable group and Q¹, Z, m, R¹ and R² are as defined in claim 1 except that any functional group is protected if necessary, with a compound of the Formula:



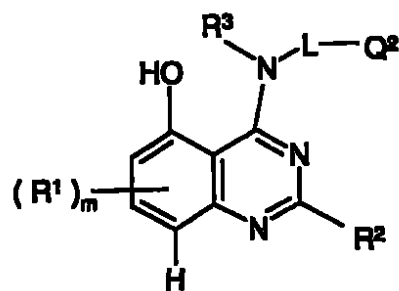
- 15 wherein Q², L and R³ are as defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means;
 or
 (b) for the production of those compounds of the Formula I wherein Z is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of an alcohol of the
 20 Formula:



wherein Q¹ is as defined in claim 1 except that any functional group is protected if necessary, with a quinazoline of the Formula VI

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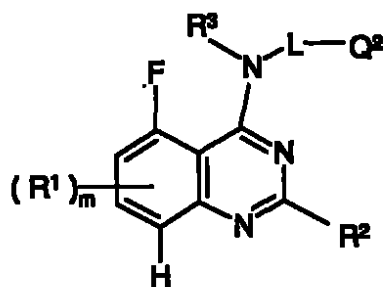
VI

wherein m , R^1 , R^2 , R^3 , L and Q^2 are as defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means; or

- 5 (c) for the production of those compounds of the formula I wherein Z is O, the reaction of an alcohol of the Formula



wherein Q^1 is as defined in claim 1 except that any functional group is protected if necessary with a quinazoline of the Formula VIII



VIII

10

wherein m , R^1 , R^2 , R^3 , L and Q^2 are as defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means; or

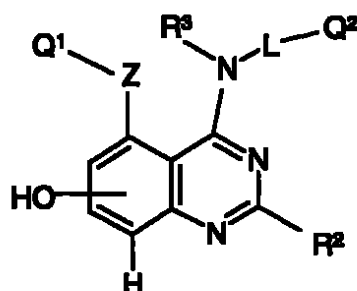
- (d) for the production of those compounds of the Formula I wherein m is 1 and R^1 is a
15 group of the formula



wherein Q^3 is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group and X^1 is O, the coupling of a quinazoline of the Formula XI

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XI

wherein Q^1 , Z , L , R^2 , R^3 and Q^2 are as defined in claim 1 except that any functional group is protected if necessary, with an alcohol of the formula Q^3OH wherein any functional group in Q^3 is protected if necessary, whereafter any protecting group that is present is removed by

5 conventional means; or

(e) for the production of those compounds of the formula I wherein R^1 is a hydroxy group, the cleavage of a quinazoline derivative of the formula I wherein R^1 is a (1-6C)alkoxy or arylmethoxy group; or

(f) for the production of those compounds of the formula I wherein Q^1 , R^1 or Q^2 contains
10 a primary or secondary amino group, the cleavage of the corresponding compound of Formula I wherein Q^1 , R^1 or Q^2 contains a protected primary or secondary amino group; or

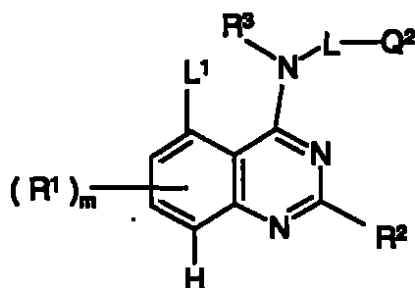
(g) for the production of those compounds of the Formula I wherein Q^1 , R^1 or Q^2 contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the alkylation of a quinazoline derivative of the formula I wherein
15 Q^1 , R^1 or Q^2 contains a hydroxy group or a primary or secondary amino group as appropriate; or

(h) for the production of those compounds of the Formula I wherein Q^1 , R^1 or Q^2 contains an amino-hydroxy-disubstituted (1-6C)alkoxy group, the reaction of a compound of the formula I wherein Q^1 , R^1 or Q^2 contains an epoxy-substituted (1-6C)alkoxy group with a
20 heterocyclyl compound or an appropriate amine; or

(i) the reaction of a quinazoline of the formula XII

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XII

wherein L^1 is a displaceable group and m , R^1 , R^2 , R^3 and Q^2 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of the Formula:



5 wherein Q^1 and Z are as defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means; or

(j) for the production of those compounds of the formula I wherein Q^1 , R^1 or Q^2 contains an amino-substituted (1-6C)alkoxy group, the reaction of a compound of the Formula I

10 wherein Q^1 , R^1 or Q^2 contains a halogeno-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine; or

(k) for the production of those compounds of the formula I wherein a heterocyclyl group in R^1 , Q^1 or Q^2 contains an S- or N-oxide the oxidation of a ring N or S atom in a compound of the formula (I); or

15 (l) for the production of those compounds of the formula I wherein Q^2 is a group of the formula 1a and :

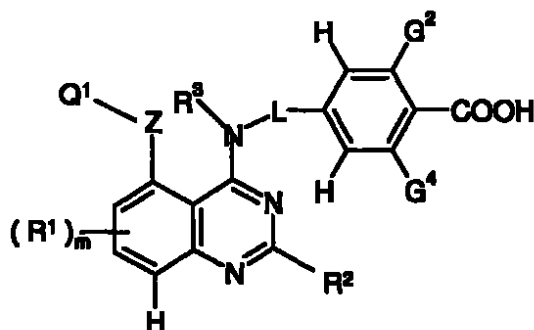
(i) G^3 is a group of the formula $CON(R^{20})Q^{10}$ wherein R^{20} and Q^{10} are as defined in claim 1, or

(ii) G^3 is a group of the formula COQ^{10} and Q^{10} is a nitrogen linked heterocyclyl

20 group, the coupling of the corresponding carboxy substituted quinazoline of the formula XIII

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XIII

- or a reactive derivative thereof, with an amine of the formula $\text{NH}(\text{R}^{20})\text{Q}^{10}$ or Q^{10}H as appropriate, wherein R^1 , R^2 , R^3 , R^{20} , Q^1 , Q^{10} , Z , L , m , G^2 and G^4 are as hereinbefore defined except that any functional group is protected if necessary, whereafter any protecting group
- 5 that is present is removed by conventional means; or
- (m) for the production of those compounds of the formula I wherein G^3 in Q^2 is a group of the formula OQ^{10} wherein Q^{10} is aryl(1-6C)alkyl, heteroaryl(1-6C)alkyl, or heteroaryl, the reaction of compound of formula I wherein G^3 in Q^2 is OH with a compound of the formula $\text{Q}^{10}\text{-L}^1$, wherein L^1 is a displaceable group, and any functional group in Q^{10} is protected if
- 10 necessary, and whereafter any protecting group that is present is removed by conventional means; or
- (n) for the production of those compounds of the formula I wherein any of Q^1 , R^1 or Q^2 contains an (2-6C)alkanoylamino, substituted (2-6C)alkanoylamino group, the acylation of a quinazoline derivative of the formula I wherein Q^1 , R^1 or Q^2 contains an amino group; or
- 15 (o) for the production of those compounds of the Formula I wherein R^1 , Q^1 or Q^2 contains an (1-6C)alkylamino or substituted (1-6C)alkylamino group or a nitrogen linked heterocyclyl group, the reductive amination of an aldehyde or ketone group in a compound of formula 1, with a (1-6C)alkylamine, substituted (1-6C)alkylamine group or a heterocycle containing an NH group in the presence of a suitable reducing agent; or
- 20 (p) the conversion of one compound of the Formula I into another compound of the Formula I;
- and when a pharmaceutically acceptable salt of a quinazoline derivative of the formula I is required it may be obtained using a conventional procedure.

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23. A pharmaceutical composition which comprises a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable thereof, as defined in claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

5 24. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined in claim 1 for use in a method of treatment of the human or animal body by therapy.

25. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable
10 salt thereof, as defined in claim 1 in the manufacture of a medicament in the prevention or treatment of tumours which are sensitive to the inhibition of one or more erbB receptor tyrosine kinases.

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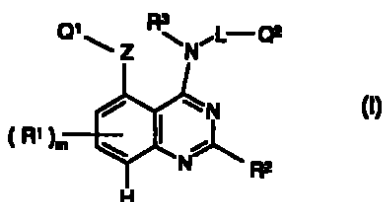
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(54) Title: QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS

(57) Abstract: The invention concerns quinazoline derivatives of Formula (I); wherein each of Q¹, Q², Z, R¹, R², R³, L and m have
any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and
their use in the manufacture of a medicament for use in the prevention or treatment of tumours which are sensitive to inhibition of
erbB receptor tyrosine kinases.

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Documentation searched other than minimum documentation is the extent that such documents are included in the fields searched

Electronic data bases consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 09294 A (WELLCOME FOUND ;HUDSON ALAN THOMAS (GB); VILE SADIE (GB); BARRACLO) 28 March 1996 (1996-03-28) cited in the application claims 1,19,26	1-25
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X	US 6 004 967 A (HIRTH KLAUS PETER ET AL) 21 December 1999 (1999-12-21) column 1, line 10 -column 3, line 49 -/-	1-25

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

10 January 2003

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	WO 98 38984 A (SUGEN INC ;SHENOY NARMADA (US); WAGNER GREGORY S (US)) 11 September 1998 (1998-09-11) claims 2,57,61	1-25
Y	WO 98 50370 A (KUTSCHER BERNHARD ;WEINBERGER HEINZ (DE); SUGEN INC (US); TANG PEN) 12 November 1998 (1998-11-12) page 53, line 5 - line 27; claim 10	1-25
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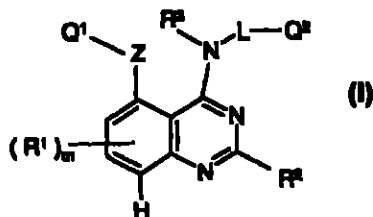
(84) Países designados (regionales): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eursialtica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(84) Título: DERIVADOS DE QUINAZOLINA COMO AGENTES ANTINEOPLÁSICOS



(57) Extracto: La invención concierne a derivados de quinazolina de Fórmula (I); en donde cada uno de Q¹, Q², Z, R¹, R², R³, L y m tienen cualquiera de los significados definidos en la descripción; procesos para su preparación, composiciones farmacéuticas que los contienen, y su uso en la manufactura de un medicamento para uso en la prevención o tratamiento de tumores que son sensibles a la inhibición de tirosina cinasas de receptor erbB.

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DERIVADOS DE QUINAZOLINA COMO AGENTES ANTINEOPLÁSICOS

La invención concierne a ciertos derivados novedosos de quinazolina, o sales farmacéuticamente aceptables de los mismos, los cuales poseen actividad antineoplásica y, en consecuencia, son útiles en métodos de tratamiento del cuerpo humano o animal. La invención atañe igualmente a procesos para la manufactura de dichos derivados de quinazolinas, a composiciones farmacéuticas que los contienen y a su uso en métodos terapéuticos, por ejemplo en la manufactura de medicamentos para empleo en la prevención o tratamiento de enfermedad de tumor sólido en un animal de sangre caliente tal como el hombre.

Muchos de los regímenes actuales de tratamiento para enfermedades resultantes de la regulación anormal de la proliferación celular, tales como psoriasis y cáncer, utilizan compuestos que inhiben la síntesis de ADN y la proliferación celular. A la fecha, los compuestos usados en tales tratamientos son generalmente tóxicos a las células; no obstante, sus efectos mejorados pueden ser benéficos en células que se dividen rápidamente, tales como las células tumorales. En la actualidad se están desarrollando metodologías alternativas a estos agentes antineoplásicos citotóxicos, por ejemplo inhibidores selectivos de vías de señalización celular. Es probable que estos tipos de inhibidores tengan el potencial de desplegar una selectividad mejorada de acción contra células tumorales y, así, es de presumir que reduzcan la probabilidad de la terapia con efectos secundarios indeseados.

Las células eucarióticas responden continuamente a múltiples señales extracelulares diversas que permiten la comunicación entre células en un organismo. Estas señales regulan una amplia variedad de respuestas físicas en la célula, incluidas la proliferación, diferenciación, apoptosis y motilidad. Las señales extracelulares adoptan la forma de una heterogénea variedad de factores solubles incluidos los factores de crecimiento, así como factores paracrinos y endocrinos. Enlazándose a receptores

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específicos de transmembrana, estos ligandos integran la señal extracelular a las vías de señalización intracelular, transluciendo en consecuencia la señal a través de la membrana plasmática y permitiendo que la célula individual responda a sus señales extracelulares. Muchos de estos procesos de transducción de señales utilizan el proceso reversible de la fosforilación de proteínas, implicadas en la promoción de estas respuestas celulares diversas. El estado de fosforilación de proteínas elegidas como dianas se regula por cinasas específicas y fosfatasas que son responsables de la regulación de aproximadamente un tercio de todas las proteínas codificadas por el genoma mamífero. Como la fosforilación es un mecanismo regulador tan importante en el proceso de transducción de señales, no es sorprendente, por lo tanto, que aberraciones en estas vías intracelulares tengan como resultado un crecimiento y diferenciación celular anormal y promuevan así la transformación celular (evaluada en Cohen *et al.*, Curr Opin Chem Biol. 1999,3, 459-465).

Se ha demostrado ampliamente que un número de estas tirosina cinasas son mutadas en formas constitutivamente activas, y/o cuando se sobreexpresan, resultan en la transformación de una variedad de células humanas. Estas formas mutadas y sobreexpresadas de la cinasa están presentes en una gran proporción de tumores humanos (evaluados en Kolibaba *et al.*, Biochimica et Biophysica Acta, 1997,133. F217-F248). Como las tirosina cinasas desempeñan un papel fundamental en la proliferación y diferenciación de una variedad de tejidos, se ha centrado una gran atención en estas enzimas en el desarrollo de novedosas terapias antineoplásicas. Esta familia de enzimas se divide en dos grupos – tirosina cinasas de receptor y tirosina cinasas de no receptor, verbigracia. Receptores EGF y la familia SRC respectivamente. A partir de los resultados de un gran número de estudios, incluido el Proyecto Genoma Humano, se han identificado alrededor de 90 tirosina cinasas en el genoma humano: de éstas 58 son del tipo receptor y 32 son del tipo no receptor. Éstas pueden clasificarse en 20 sub-familias de tirosina cinasa de receptor y 10 de tirosina cinasa de no receptor (Robinson *et al.*, Oncogene, 2000, 19,

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5548-5557).

Las tirosina cinasas de receptor son de particular importancia en la transmisión de señales mitogénicas que inician la replicación celular. Estas enormes glucoproteínas, que abarcan la membrana plasmática de la célula, poseen un dominio de fijación extracelular para sus ligandos específicos (tales como el Factor de Crecimiento Epidérmico (EGF) para el Receptor EGF). La fijación del ligando tiene como resultado la activación de la actividad enzimática cinasa del receptor que se codifica por la porción intracelular del receptor. Esta actividad fosforila aminoácidos tirosina claves en proteínas tomadas como dianas, resultando en la transducción de señales proliferantes a través de la membrana plasmática de la célula.

Se sabe que la familia erbB de tirosina cinasas de receptor, las cuales incluyen EGFR, erbB2, erbB3 y erbB4, están implicadas frecuentemente en inducir la proliferación y supervivencia de células tumorales (evaluadas en Olayioye *et al.*, EMBO J., 2000, 19, 3159). Un mecanismo en el cual puede lograrse esto es mediante la sobreexpresión del receptor en el nivel proteínico, generalmente como resultado de la amplificación de genes. Esto ha sido observado en muchos cánceres humanos comunes (evaluados en Klapper *et al.*, Adv. Cancer Res., 2000, 77, 25) tales como cáncer de mama (Sainsbury *et al.*, Brit. J. Cancer, 1988, 58, 458; Guerin *et al.*, Oncogene Res., 1988, 3, 21; Slamon *et al.*, Science, 1989, 244, 707; Klijn *et al.*, Breast Cancer Res. Treat., 1994, 29, 73 y evaluado en Salomon *et al.*, Crit. Rev. Oncol. Hematol., 1995, 19, 183), cánceres pulmonares amicrocíticos (NSCLCs) incluidos adenocarcinomas (Cerny *et al.*, Brit. J. Cancer, 1986, 54, 265; Reubi *et al.*, Int. J. Cancer, 1990, 45, 269; Rusch *et al.*, Cancer Research, 1993, 53, 2379; Brabender *et al.*, Clin. Cancer Res., 2001, 7, 1850) así como otros cánceres pulmonares (Hendler *et al.*, Cancer Cells, 1989, 7, 347; Ohsaki *et al.*, Oncol. Rep., 2000, 7, 603), cáncer de vejiga (Neal *et al.*, Lancet, 1985, 366; Chow *et al.*, Clin. Cancer Res., 2001, 7, 1957, Zhau *et al.*, Mol Carcinog., 3, 254), cáncer esofágico (Mukaida *et al.*, Cancer, 1991, 68, 142), cáncer gastrointestinal tal como cáncer de colon, rectal o gástrico (Bolen *et al.*, Oncogene Res., 1987, 1, 149; Kapitanovic *et*

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al., Gastroenterology, 2000, 112, 1103; Ross et al., Cancer Invest., 2001, 19, 554), cáncer de la próstata (Visakorpi et al., Histochem. J., 1992, 24, 481; Kumar et al., 2000, 32, 73; Scher et al., J. Natl. Cancer Inst., 2000, 92, 1866), leucemia (Konaka et al., Cell, 1984, 37, 1035, Martin-Subero et al., Cancer Genet Cytogenet., 2001, 127, 174), ovárico (Hellstrom et al., Cancer Res., 2001, 61, 2420), de cabeza y cuello (Shiga et al., Head Neck, 2000, 22, 599) o cáncer pancreático (Ovotny et al., Neoplasma, 2001, 48, 188). En la medida en que se estudien más tejidos tumorales humanos para detectar la expresión de la familia erbB de tirosina cinasas de receptor, se espera que su prevalencia e importancia, ampliamente difundidas, se intensificarán aún más en el futuro.

Como consecuencia de esta regulación incorrecta de uno o más de estos receptores (en particular, erbB2), se cree en gran medida que muchos tumores se vuelven clínicamente más intensivos y, por lo tanto, se correlacionan con un pronóstico más inadecuado para el paciente (Brabender et al., Clin. Cancer Res., 2001, 7, 1850; Ross et al., Cancer Investigation, 2001, 19, 554, Yu et al., Bioessays, 2000, 22.7, 673). Aparte de estos descubrimientos clínicos, una profusión de información pre-clínica sugiere que la familia erbB de tirosina cinasas de receptor se encuentra implicada en la transformación celular. Esto incluye las observaciones de que muchas estirpes celulares tumorales sobreexpresan uno o más de los receptores erbB y que EGFR o erbB2, cuando se transfectan en células no tumorales, tienen la capacidad de transformar estas células. Este potencial tumorigénico ha sido verificado además pues ratones transgénicos, que sobreexpresan erbB2 espontáneamente, desarrollan tumores en la glándula mamaria. Además, un número de estudios pre-clínicos han demostrado que pueden inducirse efectos antiproliferantes eliminando una o más actividades erbB mediante inhibidores de moléculas pequeñas, anticuerpos negativos o inhibidores dominantes (evaluados en Mendelsohn et al., Oncogene, 2000, 19, 6550). Se ha reconocido, en consecuencia, que los inhibidores de estas tirosina cinasas de receptor deben ser valiosos como un inhibidor selectivo de la proliferación de células cancerosas de mamífero (Yaish et al.,

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Science, 1988, 242, 933, Kolibaba *et al.*, Biochimica et Biophysica Acta, 1997, 133, F217-F248; Al-Obeidi *et al.*, 2000, Oncogene, 19, 5690-5701; Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565). Aparte de estos datos pre-clínicos, los hallazgos que emplean anticuerpos inhibidores contra EGFR y erbB2 (c-225 y trastuzumab respectivamente) han demostrado ser benéficos en la clínica para el tratamiento de tumores sólidos seleccionados (evaluados en Mendelsohn *et al.*, 2000, Oncogene, 19, 6550-6565).

Se ha detectado la amplificación y/o actividad de miembros de las tirosina cinasas de receptor del tipo ErbB y, así, se han implicado en desempeñar un papel en un número de trastornos proliferantes no malignos tales como psoriasis (Ben-Bassat, Curr. Pharm. Des., 2000, 6, 933; Elder *et al.*, Science, 1989, 243, 811), hiperplasia prostática benigna (BPH) (Kumar *et al.*, Int. Urol. Nephrol., 2000, 32, 73), aterosclerosis y restenosis (Bokemeyer *et al.*, Kidney Int., 2000, 58, 549). Se espera, en consecuencia, que inhibidores de tirosina cinasas de receptor tipo erbB serán útiles en el tratamiento de estos y otros trastornos no malignos de proliferación celular excesiva.

Las Solicitudes de Patente Internacional WO 96/33977, WO 96/33978, WO 96/33979, WO 96/33980 y WO 96/33981 divulgan que ciertos derivados de quinazolina con un sustituyente anilino en la posición 4 poseen actividad inhibidora de tirosina cinasa de receptor.

Una evaluación de la relación actividad/estructura de varios derivados de quinazolina se divulga por G. W. Rewcastle *et al.* (J. Med. Chem. 1995, 38, 3428-3487), incluido un número de compuestos 5-sustituidos. No obstante, se afirma que tales compuestos 5-sustituidos tienen una baja actividad in-vitro como inhibidores de tirosina cinasa EGFR comparada con quinazolinas sustituidas en las posiciones 6 y 7.

WO 96/09294 divulga derivados de 4-anilinoquinazolina, incluidos derivados de quinazolina 5-cloro y 5-metoxi sustituida, como inhibidores de proteína tirosina cinasa.

La Solicitud de Patente Internacional Co-pendiente PCT/GB01/02424 divulga que ciertos derivados de quinazolinas con un 5-sustituyente son

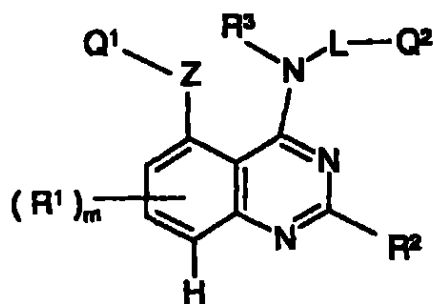
inhibidores de la familia Src de tirosina cinasas de no receptor, tales como c-Src, c-Yes y C-Fyn.

Inesperadamente hemos encontrado ahora que ciertos derivados de quinazolina 5-sustituida poseen potente actividad antineoplásica. Sin querer implicar que los compuestos divulgados en la presente invención poseen actividad farmacológica tan solo en virtud de un efecto sobre un proceso biológico único, se cree que los compuestos proveen un efecto antineoplásico mediante la inhibición de una o más de la familia de tirosina cinasas de receptor, que se encuentran implicadas en los pasos de transducción de señales, que llevan a la proliferación de células tumorales. En particular, se cree que los compuestos de la presente invención proveen un efecto antineoplásico mediante la inhibición de tirosina cinasas de receptor EGFR y/o erbB2.

Generalmente los compuestos de la presente invención poseen potente actividad inhibidora contra la familia de tirosina cinasa de receptor erbB, por ejemplo, mediante inhibición de tirosina cinasas de receptor EGFR y/o erbB2 y/o erbB4, poseyendo al mismo tiempo actividad inhibidora menos potente contra otras cinasas. Más aún, ciertos compuestos de la presente invención poseen una potencia sustancialmente mejor contra la tirosina cinasa erbB2 sobre la de la EGFR, proveyendo así en forma potencial un tratamiento efectivo para tumores inducidos por erbB2. Adicionalmente, algunos de los compuestos de acuerdo con la presente invención poseen una potencia sustancialmente mejor contra la tirosina cinasa EGFR sobre la de la erbB2. La invención incluye asimismo compuestos que son activos contra todas o una combinación de tirosina cinasas de receptor EGFR, erbB2 y erbB4, proveyendo así potencialmente tratamientos para afecciones mediadas por una o más de estas tirosina cinasas de receptor.

De acuerdo con un primer aspecto de la invención se provee un derivado de quinazolina de la Fórmula I

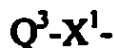
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en donde m es 0, 1 ó 2;

cada grupo R^1 , que puede ser el mismo o diferente, se selecciona de halógeno, trifluorometilo, ciano, isociano, nitro, hidroxilo, mercapto, amino, formilo, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N -(1-6C)alquilcarbamoilo, N,N -di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N -(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N -(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N -(1-6C)alquil-(3-6C)alquinoilamino, N -(1-6C)alquilsulfamoilo, N,N -di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N -(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



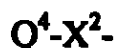
en donde X^1 es un enlace directo o se selecciona de O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ y N(R⁴)C(R⁴)₂, en donde cada R⁴ es, independientemente, hidrógeno o (1-6C)alquilo, y Q^3 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo, o $(R^1)_m$ es (1-3C)alquilenodioxo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R⁵),

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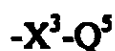
CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH y C≡C en donde R⁵ es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo CH₂=CH- o HC≡C- en un sustituyente R¹ lleva opcionalmente en la posición terminal CH₂= o HC≡ un sustituyente seleccionado de halógeno, carboxi, carbamoilo, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquilo o de un grupo de la fórmula:



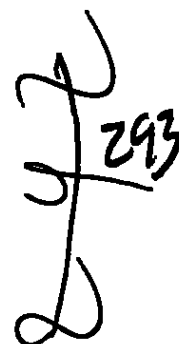
en donde X² es un enlace directo o se selecciona de CO y N(R⁶)CO, en donde R⁶ es hidrógeno o (1-6C)alquilo, y Q⁴ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicli-(1-6C)alquilo,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R¹ lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ uno o más sustituyentes halógeno o (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X³ es un enlace directo o se selecciona de O, S, SO, SO₂, N(R⁷), CO, CH(OR⁷), CON(R⁷), N(R⁷)CO, SO₂N(R⁷), N(R⁷)SO₂, C(R⁷)₂O, C(R⁷)₂S y N(R⁷)C(R⁷)₂, en donde R⁷ es hidrógeno o (1-6C)alquilo, y Q⁵ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicli-(1-6C)alquilo,

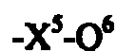
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y en donde cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en R¹ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, amino(2-6C)alcanoilo, N-(1-6C)alquilamino(2-6C)alcanoilo, N,N-di-[(1-6C)alquil]amino(2-6C)alcanoilo, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X⁴ es un enlace directo o se selecciona de O y N(R⁹), en donde R⁹ es hidrógeno o (1-6C)alquilo, y R⁸ es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, carboxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo, (1-6C)alcoxycarbonilamino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X⁵ es un enlace directo o se selecciona de O, CO y N(R¹⁰), en donde R¹⁰ es hidrógeno o (1-6C)alquilo, y Q⁶ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

y en donde cualquier grupo heterociclilo en un sustituyente en R¹

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lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

R^2 es hidrógeno;

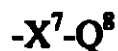
R^3 es hidrógeno o (1-6C)alquilo;

Z es un enlace directo o se selecciona de O, S, SO, SO₂, N(R¹¹), CO, CH(OR¹¹), CON(R¹¹), N(R¹¹)CO, SO₂N(R¹¹), N(R¹¹)SO₂, OC(R¹¹)₂, SC(R¹¹)₂ y N(R¹¹)C(R¹¹)₂, en donde cada R¹¹ es, independientemente, hidrógeno o (1-6C)alquilo;

Q¹ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en el grupo Q¹-Z- se separa opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R¹²), CO, CH(OR¹²), CON(R¹²), N(R¹²)CO, SO₂N(R¹²), N(R¹²)SO₂, CH=CH y C≡C en donde R¹² es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q¹-Z- lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



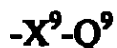
en donde X⁷ es un enlace directo o se selecciona de O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S y N(R¹⁴)C(R¹⁴)₂, en donde R¹⁴ es hidrógeno o (1-6C)alquilo, y Q⁸ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-

6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, amino(2-6C)alcanoilo, N-(1-6C)alquilamino(2-6C)alcanoilo, N,N-di-[(1-6C)alquil]amino(2-6C)alcanoilo, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X⁸ es un enlace directo o se selecciona de O y N(R¹⁶), en donde R¹⁶ es hidrógeno o (1-6C)alquilo, y R¹⁵ es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alkylamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxicarbonil-(1-6C)alquilo, o de un grupo de la fórmula:



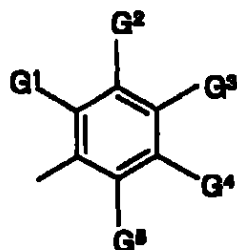
en donde X⁹ es un enlace directo o se selecciona de O, CO y N(R¹⁷), en donde R¹⁷ es hidrógeno o (1-6C)alquilo, y Q⁹ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-

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6C)alcoxi,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

Q² es un grupo arilo de fórmula Ia



Ia

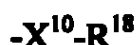
en donde G¹ y G⁵ son hidrógeno,

G² y G⁴ cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino, arilo y heteroarilo,

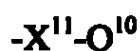
y en donde un grupo arilo o heteroarilo en cualquiera de G² y G⁴ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

G³ se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N-N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-

6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

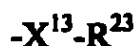


en donde X^{10} es un enlace directo o se selecciona de O y N(R¹⁹), en donde R¹⁹ es hidrógeno o (1-6C)alquilo, y R¹⁸ es halógeno-(1-6C)alquil hidroxil-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO, SO₂, N(R²⁰), CO, CH(OR²⁰), CON(R²⁰), N(R²⁰)CO, SO₂N(R²⁰), N(R²⁰)SO₂, C(R²⁰)₂O, C(R²⁰)₂S, C(R²⁰)₂N(R²⁰) y N(R²⁰)C(R²⁰)₂, en donde R²⁰ es hidrógeno o (1-6C)alquilo, y Q¹⁰ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde Q¹⁰ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxil, amino, carboxil, formil, carbamoilo, sulfamoilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^{13} es un enlace directo o se selecciona de O y N(R²⁴), en donde R²⁴ es hidrógeno o (1-6C)alquilo, y R²³ es halógeno-(1-6C)alquilo, hidroxil-

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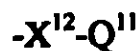
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(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en Q¹⁰ lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,

o G³ y G⁴ juntos forman un grupo de fórmula :- -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-, -CH=N-CH=N-, -N=CH-CH=N-, -N=N-CH=CH-, -CH=CH-N=N-, -CH=CH-O-, -O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH₂-CH₂-O-, -O-CH₂-CH₂-, -CH₂-CH₂-S-, -S-CH₂-CH₂-, -O-CH₂-O-, -O-CH₂-CH₂-O-, -S-CH₂-S-, -S-CH₂-CH₂-S-, -CH=CH-NH-, -NH-CH=CH-, -CH₂-CH₂-NH-, -NH-CH₂-CH₂-, -N=CH-NH-, -NH-CH=N-, -NH-CH₂-NH-, -O-CH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH₂-NH-, -NH-CH₂-O-, -S-CH₂-NH-, -NH-CH₂-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -CH=N-S-, -O-NH-CH₂-, -CH₂-NH-O-, -S-NH-CH₂-, -CH₂-NH-S-, -NH-N=CH-, -CH=N-NH-, -NH-NH-CH₂-, -CH₂-NH-NH-, -N=N-NH- o -NH-N=N-,

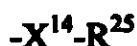
y el anillo heteroarilo o heterocíclico, bicíclico, de 9 o 10 miembros, formado cuando G³ y G⁴ juntos se enlazan lleva opcionalmente en la porción heteroarilo o heterocíclica del anillo bicíclico 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino y un grupo de la fórmula:



en donde X¹² es un enlace directo o se selecciona de O, SO, SO₂, N(R²¹), SO₂N(R²¹) y CO, en donde R²¹ es hidrógeno o (1-6C)alquil y Q¹¹ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que

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pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, formilo, carbamoilo, sulfamoilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

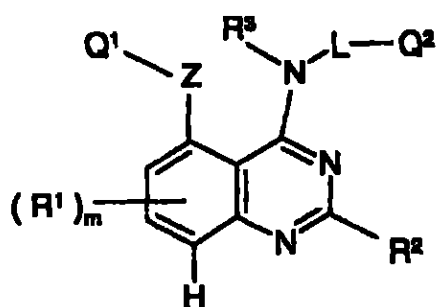


en donde X^{14} es un enlace directo o se selecciona de O y N(R^{26}), en donde R^{26} es hidrógeno o (1-6C)alquilo, y R^{25} es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo, (2-6C)alcanoilo-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo; y

L es un enlace directo o $-[C(R^{22})_2]_n$, en donde n es 1 ó 2, y cada R^{22} independientemente es hidrógeno o (1-4C)alquilo,

y cuando **L** es un enlace directo, por lo menos uno de G^2 , G^3 y G^4 es distinto de H; o una sal farmacéuticamente aceptable del mismo.

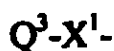
De acuerdo con un aspecto adicional de la presente invención se provee un derivado de quinazolina de la Fórmula I.



I

en donde m es 0, 1 ó 2;

cada grupo R^1 , que puede ser el mismo o diferente, se selecciona de halógeno, trifluorometilo, ciano, isociano, nitro, hidroxilo, mercapto, amino, formilo, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alquenilo, (2-6C)alquinilo, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N -(1-6C)alquilcarbamoilo, N,N -di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N -(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N -(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N -(1-6C)alquil-(3-6C)alquinoilamino, N -(1-6C)alquilsulfamoilo, N,N -di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N -(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

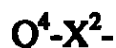


en donde X^1 es un enlace directo o se selecciona de O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ y N(R⁴)C(R⁴)₂, en donde cada R⁴ es, independientemente, hidrógeno o (1-6C)alquilo, y Q³ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenal-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo, o (R¹)_m es (1-3C)alquilenodioxo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH y C≡C en donde R⁵ es hidrógeno o (1-6C)alquilo,

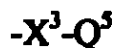
y en donde cualquier grupo CH₂=CH- ó HC≡C- en un sustituyente R¹ lleva opcionalmente en la posición terminal CH₂= ó HC≡ un sustituyente seleccionado de halógeno, carboxi, carbamoilo, (1-6C)alcoxycarbonilo, N -(1-6C)alquilcarbamoilo, N,N -di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-

6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquil o de un grupo de la fórmula:



en donde X^2 es un enlace directo o se selecciona de CO y $N(R^6)CO$, en donde R^6 es hidrógeno o (1-6C)alquilo, y Q^4 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O, S, SO, SO_2 , $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ y $N(R^7)C(R^7)_2$, en donde R^7 es hidrógeno o (1-6C)alquilo, y Q^5 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo,

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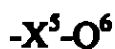


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(1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^4 es un enlace directo o se selecciona de O y N(R^9), en donde R^9 es hidrógeno o (1-6C)alquilo, y R^8 es halógeno-(1-6C)alquilo, hidroxí-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo o (1-6C)alcoxycarbonilamino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^5 es un enlace directo o se selecciona de O, CO y N(R^{10}), en donde R^{10} es hidrógeno o (1-6C)alquilo, y Q^6 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclíl-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

R^2 es hidrógeno;

R^3 es hidrógeno o (1-6C)alquilo;

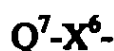
Z es un enlace directo o se selecciona de O, S, SO, SO₂ N(R^{11}), CO, CH(OR¹¹), CON(R^{11}), N(R^{11})CO, SO₂N(R^{11}), N(R^{11})SO₂, OC(R^{11})₂, SC(R^{11})₂ y N(R^{11})C(R^{11})₂, en donde cada R^{11} es, independientemente, hidrógeno o (1-6C)alquilo;

Q^1 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclíl-(1-6C)alquilo,

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y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en el grupo Q^1-Z se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R¹²), CO, CH(OR¹²), CON(R¹²), N(R¹²)CO, SO₂N(CR¹²), N(R¹²)SO₂, CH=CH y C≡C en donde R¹² es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo CH₂=CH- ó HC≡C- en el grupo Q^1-Z lleva opcionalmente en la posición terminal CH₂= ó HC≡ un sustituyente seleccionado de halógeno, carboxi, carbamoilo, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquil o de un grupo de la fórmula:



en donde X⁶ es un enlace directo o se selecciona de CO y N(R¹³)CO, en donde R¹³ es hidrógeno o (1-6C)alquilo, y Q⁷ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q^1-Z lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ uno o más sustituyentes halógeno o (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



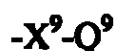
en donde X⁷ es un enlace directo o se selecciona de O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S y N(R¹⁴)C(R¹⁴)₂, en donde R¹⁴ es hidrógeno o (1-6C)alquilo, y Q⁸ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-

6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X⁸ es un enlace directo o se selecciona de O y N(R¹⁶), en donde R¹⁶ es hidrógeno o (1-6C)alquilo, y R¹⁵ es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



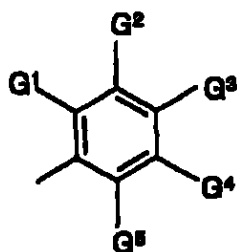
en donde X⁹ es un enlace directo o se selecciona de O, CO y N(R¹⁷), en donde R¹⁷ es hidrógeno o (1-6C)alquilo, y Q⁹ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

Q² es un grupo arilo de fórmula Ia

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Ia

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en donde G^1 y G^5 son hidrógeno,

G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino, arilo y heteroarilo,

y en donde un grupo arilo o heteroarilo en cualquiera de G^2 y G^4 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

G^3 se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

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en donde X^{10} es un enlace directo o se selecciona de O y N(R^{19}), en donde R^{19} es hidrógeno o (1-6C)alquilo, y R^{18} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO, SO₂, N(R^{20}), CO, CH(OR²⁰), CON(R^{20}), N(R^{20})CO, SO₂N(R^{20}), N(R^{20})SO₂, C(R^{20})₂O, C(R^{20})₂S y N(R^{20})C(R^{20})₂, en donde R^{20} es hidrógeno o (1-6C)alquilo, y Q^{10} es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicli-(1-6C)alquilo,

y en donde Q^{10} lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino,

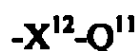
y en donde cualquier grupo heterociclilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,

o G^3 y G^4 juntos forman un grupo de fórmula: -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-, -CH=N-CH=N-, -N=CH-CH=N-, -N=N-CH=CH-, -CH=CH-N=N-, -CH=CH-O-, -O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH₂-CH₂-O-, -O-CH₂-CH₂-, -CH₂-CH₂-S-, -S-CH₂-CH₂-, -O-CH₂-O-, -O-

CH₂-CH₂-O-, -S-CH₂-S-, -S-CH₂-CH₂-S-, -CH=CH-NH-, -NH-CH=CH-, -CH₂-CH₂-NH-, -NH-CH₂-CH₂-, -N=CH-NH-, -NH-CH=N-, -NH-CH₂-NH-, -O-CH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH₂-NH-, -NH-CH₂-O-, -S-CH₂-NH-, -NH-CH₂-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -CH=N-S-, -O-NH-CH₂-, -CH₂-NH-O-, -S-NH-CH₂-, -CH₂-NH-S-, -NH-N=CH-, -CH=N-NH-, -NH-NH-CH₂-, -CH₂-NH-NH-, -N=N-NH- ó -NH-N=N-,

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y el anillo heteroarilo o heterocíclico, bicíclico, de 9 o 10 miembros, formado cuando G³ y G⁴ juntos se enlazan, lleva opcionalmente en la porción heteroarilo o heterocíclica del anillo bicíclico 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, o de un grupo de la fórmula:



en donde X¹² es un enlace directo o se selecciona de O, SO, SO₂, N(R²¹) y CO, en donde R²¹ es hidrógeno o (1-6C)alquilo y Q¹¹ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterocíclico o heterocíclico-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi, y cualquier anillo heterocíclico bicíclico así formado lleva opcionalmente 1 ó 2 grupos oxo o tioxo; y

L es un enlace directo o -[C(R²²)₂]_n-, en donde n es 1 ó 2, y cada R²² independientemente es hidrógeno o (1-4C)alquilo,

y cuando L es un enlace directo, por lo menos uno de G², G³ y G⁴ es distinto de H; o una sal farmacéuticamente aceptable del mismo.

De acuerdo con un aspecto adicional de la invención se provee un derivado de quinazolina de la Fórmula I en donde cada uno de m, R¹, R², R³, L y Q² tiene cualquiera de los significados definidos arriba en el texto y

Z se selecciona de O, S, SO, SO₂, N(R¹¹), CO, CH(OR¹¹), CON(R¹¹), N(R¹¹)CO, SO₂N(R¹¹), N(R¹¹)SO₂, OC(R¹¹)₂, SC(R¹¹)₂ y N(R¹¹)C(R¹¹)₂, en

donde R^{11} es hidrógeno o (1-6C)alquilo; y

Q^1 se selecciona de (3-7C)cicloalquilo, (3-7C)cicloalquenilo y heterociclilo,

y en donde cualquier grupo CH_2 ó CH_3 en el grupo Q^1 -Z- lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^7 es un enlace directo o se selecciona de O, S, SO, SO_2 , $N(R^{14})$, CO, $CH(OR^{14})$, $CON(R^{14})$, $N(R^{14})CO$, $SO_2N(R^{14})$, $N(R^{14})SO_2$, $C(R^{14})_2O$, $C(R^{14})_2S$ y $N(R^{14})C(R^{14})_2$, en donde R^{14} es hidrógeno o (1-6C)alquilo, y Q^8 es (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenal-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en el grupo Q^1 -Z- lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, amino(2-6C)alcanoilo, N-(1-6C)alquilamino(2-6C)alcanoilo, N,N-di-[(1-6C)alquil]amino(2-6C)alcanoilo, N-(1-

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6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^8 es un enlace directo o se selecciona de O y N(R^{16}), en donde R^{16} es hidrógeno o (1-6C)alquilo, y R^{15} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^9 es un enlace directo o se selecciona de O, CO y N(R^{17}), en donde R^{17} es hidrógeno o (1-6C)alquilo, y Q^9 es heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi, y en donde cualquier grupo heterociclilo en el grupo Q^1 -Z- lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo.

De acuerdo con un aspecto adicional de la invención se provee un derivado de quinazolina de la Fórmula I en donde cada uno de m, R^1 , R^2 , R^3 , L y Q^2 tiene cualquiera de los significados definidos arriba en el texto y Z se selecciona de O, S, SO, SO₂, N(R^{11}), CO, CH(OR¹¹), CON(R^{11}), N(R^{11})CO, SO₂N(R^{11}), N(R^{11})SO₂, OC(R^{11})₂, SC(R^{11})₂ y N(R^{11})C(R^{11})₂, en donde cada R^{11} es hidrógeno o (1-6C)alquilo; y

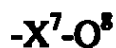
Q^1 es (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en el grupo Q^1 -Z- se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R^{12}), CO,

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CH(OR¹²), CON(R¹²), N(R¹²)CO, SO₂N(R¹²), N(R¹²)SO₂, CH=CH y C≡C en donde R¹² es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q¹-Z- lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ uno o más sustituyentes halógeno o (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X⁷ es un enlace directo o se selecciona de O, S, SO, SO₂, N(R¹⁴), CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S y N(R¹⁴)C(R¹⁴)₂, en donde R¹⁴ es hidrógeno o (1-6C)alquilo, y Q⁸ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

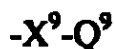
y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C) alcanosulfonilamino y N-(1-6C)alquil-(1-

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6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^8 es un enlace directo o se selecciona de O y N(R^{16}), en donde R^{16} es hidrógeno o (1-6C)alquilo, y R^{15} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



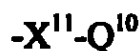
en donde X^9 es un enlace directo o se selecciona de O, CO y N(R^{17}), en donde R^{17} es hidrógeno o (1-6C)alquilo, y Q^9 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo en el grupo Q^1-Z lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo.

De acuerdo con un aspecto adicional de la invención se provee un derivado de quinazolina de la Fórmula I como se define arriba en el texto en donde m no es 0 cuando:

Z es un enlace directo o se selecciona de O, S y N(R^{11}), en donde R^{11} es como se define arriba en el texto; y

(i) L es un enlace directo, y Q^2 es un grupo arilo de la fórmula 1a como se define arriba en el texto en donde G^3 es un grupo de la fórmula:



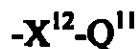
en donde X^{11} es un enlace directo o se selecciona de O, S, SO, SO₂, N(R^{20}), CH(OR²⁰), CON(R^{20}), N(R^{20})CO, SO₂N(R^{20}), N(R^{20})SO₂, C(R^{20})₂O, C(R^{20})₂S, CO y C(R^{20})₂N(R^{20}), en donde cada R^{20} es como se define arriba en el texto, y Q^{10} es arilo, aril(1-6C)alquilo, heteroarilo, o heteroaril(1-6C)alquilo; o

(ii) L es un enlace directo, y Q^2 es un grupo arilo de la fórmula 1a como se define arriba en el texto en donde G^3 es $-X^{11}-Q^{10}$, en donde X^{11} es CO y Q^{10} es un grupo heterociclilo que contiene nitrógeno, enlazado a X^{11}

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por un átomo de nitrógeno; o

(iii) L es un enlace directo, y Q² es un grupo arilo de la fórmula 1a como se define arriba en el texto en donde G³ y G⁴ juntos forman un grupo de la fórmula -NH-CH=CH-, -CH=CH-NH-, -NH-N=CH- o -CH=N-NH-, grupo que se sustituye en un grupo NH por un grupo de la fórmula:



en donde X¹² es un enlace directo o se selecciona de SO₂, CO, SO₂N(R²¹), en donde R²¹ es como se define arriba en el texto y Q¹¹ es arilo, aril(1-6C)alquilo, heteroarilo, o heteroaril (1-6C)alquilo.

En este aspecto la invención se prefiere que cuando Z es un enlace directo o se selecciona de O, S y N(R¹¹), en donde R¹¹ es como se define arriba en el texto y se satisface una cualquiera de las condiciones (i), (ii) o (iii) definidas arriba, ese m es 1 y R¹ se localiza en la posición 7, en donde R¹ es como se define arriba en el texto.

En esta especificación el término genérico "alquilo" incluye los dos grupos alquilo de cadena recta o ramificada tales como grupos propilo, isopropilo y tert-butilo, y (3-7C)cicloalquilo tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo. No obstante, las referencias a grupos alquilo individuales tales como "propilo" son específicas de la versión de cadena recta únicamente, las referencias a grupos alquilo individuales de cadena ramificada tales como "isopropilo" son específicos de la versión de cadena ramificada únicamente y las referencias a grupo cicloalquilo individuales tales como "ciclopentilo" son específicos de ese anillo de 5 miembros únicamente. Una convención análoga se aplica a otros términos genéricos, por ejemplo (1-6C)alcoxi incluye metoxi, etoxi, ciclopropiloxi y ciclopentiloxi, (1-6C)alquilamino incluye metilamino, etilamino, ciclobutilamino y ciclohexilamino, y di-[(1-6C)alquil]amino incluye dimetilamino, dietilamino, N-ciclobutil-N-metilamino y N-ciclohexil-N-etilamino.

Hay que entender que, por cuanto algunos de los compuestos de fórmula I definidos arriba pueden existir en formas ópticamente activas o

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racémicas en virtud de uno o más átomos de carbono asimétricos, la invención incluye en su definición cualquier forma semejante ópticamente activa o racémica, que posee la actividad arriba mencionada. La síntesis de formas ópticamente activas puede llevarse a cabo por técnicas estándar de química orgánica por técnicas estándar de química orgánica bien conocidas en el arte, por ejemplo mediante síntesis de materiales iniciales ópticamente activos o mediante resolución de una forma racémica. Análogamente, la actividad arriba mencionada puede evaluarse usando las técnicas de laboratorio referidas más adelante.

Hay que entender que la presente invención incluye en su definición cualquiera y todas las formas tautoméricas de los compuestos de la Fórmula I que poseen la actividad arriba mencionada.

Hay que entender también que en la medida en que ciertos compuestos de la Fórmula I pueden existir en formas solvatadas así como formas no solvatadas, por ejemplo, formas hidratadas, la presente invención incluye cualquiera y todas formas solvatadas semejantes, que poseen la actividad ya mencionada.

Valores apropiados para los radicales genéricos mencionados arriba incluyen los expuestos más abajo. Un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 , Q^3 a Q^{11}), G^2 ó G^4 cuando éste es arilo o para el grupo arilo en un grupo 'Q' es, por ejemplo, fenilo o naftilo, preferiblemente fenilo.

Un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 , Q^3 a Q^8 y Q^{10}) cuando éste es (3-7C)cicloalquilo o para el grupo (3-7C)cicloalquilo en un grupo 'Q' es, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo o biciclo[2.2.1]heptilo y un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 , Q^3 a Q^8 y Q^{10}) cuando éste es (3-7C)cicloalquenilo o para el grupo (3-7C)cicloalquenilo en un grupo 'Q' es, por ejemplo, ciclobutenilo, ciclopentenilo, ciclohexenilo o cicloheptenilo.

Un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 , Q^3 a Q^{11}), G^2 ó G^4 cuando éste es heteroarilo o para el grupo heteroarilo en un

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grupo 'Q' es, por ejemplo, un anillo monocíclico de 5 ó 6 miembros, aromático, o un anillo bicíclico de 9 ó 10 miembros con hasta cinco heteroátomos de anillo seleccionados de oxígeno, nitrógeno y azufre, los cuales, a menos que se especifique lo contrario, pueden enlazarse a carbono o nitrógeno. Ejemplos de valores apropiados de "heteroarilo" incluyen furilo, pirrolilo, tienilo, oxazolilo, isoxazolilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, 1,3,5-triazenilo, 1,3-benzodioxolilo, benzofuranilo, indolilo, benzotienilo, benzoxazolilo, benzimidazolilo, benzotiazolilo, indazolilo, benzofurazanilo, quinolilo, isoquinolilo, quinazolinilo, quinoxalinilo, cinnolinilo o naftiridinilo.

Un valor apropiado para uno cualquiera de los grupos 'Q' (Q¹, Q³ a Q¹¹) cuando éste es heterociclilo o para el grupo heterociclilo en un grupo 'Q' es, por ejemplo, un anillo monocíclico o bicíclico de 3 a 10 miembros, saturados o parcialmente saturados, no aromáticos, con hasta cinco heteroátomos seleccionados de oxígeno, nitrógeno y azufre, los cuales, a menos que se especifique lo contrario, pueden enlazarse a carbono o nitrógeno. Ejemplos de valores apropiados de "heterociclilo" incluyen oxiranilo, oxetanilo, azetidino, tetrahydrofuranilo, tetrahydropiranilo, oxepanilo, pirrolinilo, pirrolidinilo, morfolinilo, tetrahydro-1,4-tiazinilo, 1,1-dioxotetrahydro-1,4-tiazinilo, piperidinilo, homopiperidinilo, piperazinilo, homopiperazinilo, dihidropiridinilo, tetrahydropiridinilo, dihidropirimidinilo, tetrahydropirimidinilo, tetrahydrotienilo, tetrahydrotiopiranilo, decahydroisoquinolinilo o decahydroquinolinilo, preferiblemente tetrahydrofuranilo, tetrahydropiranilo, pirrolidinilo, morfolinilo, 1,4-oxazepanilo, tiamorfolinilo 1,1-dioxotetrahydro-4H-1,4-tiazinilo, piperidinilo o piperazinilo, más preferiblemente tetrahydrofuran-3-ilo, tetrahydropiran-4-ilo, tetrahydrotien-3-ilo, tetrahydrotiopiran-4-ilo, pirrolidin-3-ilo, morfolino, 1,1-dioxotetrahydro-4H-1,4-tiazin-4-ilo, piperidino, piperidin-4-ilo, piperidin-3-ilo o piperazin-1-ilo. Un átomo de nitrógeno o azufre en un grupo heterociclilo puede oxidarse para producir el correspondiente óxido N o S, por ejemplo 1,1-dioxotetrahydrotienilo, 1-

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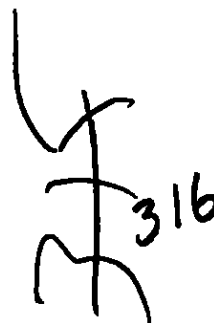
oxotetrahidrotienilo, 1,1-dioxotetrahidrotiopiranilo o 1-oxotetrahidrotiopiranilo. Un valor apropiado para un grupo semejante que lleva 1 ó 2 sustituyentes oxo o tioxo es, por ejemplo, 2-oxopirrolidinilo, 2-tioxopirrolidinilo, 2-oxoimidazolidinilo, 2-tioxoimidazolidinilo, 2-oxopiperidinilo, 2,5-dioxopirrolidinilo, 2,5-dioxoimidazolidinilo o 2,6-dioxopiperidinilo.

Un valor apropiado para un grupo 'Q' cuando éste es heteroaril-(1-6C)alquilo es, por ejemplo, heteroarilmetilo, 2-heteroariletilo y 3-heteroarilpropilo. La invención comprende los correspondientes valores apropiados para grupos 'Q' cuando, por ejemplo, en lugar de un grupo heteroaril-(1-6C)alquilo, está presente un grupo aril-(1-6C)alquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenil-(1-6C)alquilo o heterociclil-(1-6C)alquilo.

Valores apropiados para cualquiera de los grupos 'R' (R^1 a R^{26}), o para varios grupos en un sustituyente R^1 , o para G^3 o para varios grupos en G^3 , o para cualquiera de los otros 'G' (G^1 , G^2 ó G^4) en Q^2 , o para varios grupos en Q^2 , o para Q^1 o para varios grupos en Q^1 , o para varios grupos en el grupo Q^1 -Z- incluyen:-

para halógeno	fluoro, cloro, bromo y iodo;
para (1-6C)alquilo:	metilo, etilo, propilo, isopropilo y <u>tert</u> -butilo;
para (2-8C)alquenilo:	vinilo, isopropenilo, alilo y but-2-enilo;
para (2-8C)alquinilo:	etinilo, 2-propinilo y but-2-inilo;
para (1-6C)alcoxi:	metoxi, etoxi, propoxi, isopropoxi y butoxi;
para (2-6C)alqueniloxi:	viniloxi y aliloxi;
para (2-6C)alquiniloxi:	etiniloxi y 2-propiniloxi;

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para (1-6C)alquiltio:	metiltio, etiltio y propiltio;
para (1-6C)alquilsulfinilo:	metilsulfinilo y etilsulfinilo;
para (1-6C)alquilsulfonilo:	metilsulfonilo y etilsulfonilo;
para (1-6C)alquilamino:	metilamino, etilamino, propilamino, isopropilamino y butilamino;
para di-[(1-6C)alquil]amino:	dimetilamino, dietilamino, <u>N</u> -etil- <u>N</u> -metilamino y diisopropilamino;
para (1-6C)alcoxycarbonilo:	metoxycarbonilo, etoxycarbonilo, propoxycarbonilo y tert-butoxycarbonilo;
para <u>N</u> -(1-6C)alquilcarbamoilo:	<u>N</u> -metilcarbamoilo, <u>N</u> -etilcarbamoilo y <u>N</u> -propilcarbamoilo;
para <u>N,N</u> -di-[(1-6C)alquil]carbamoilo:	<u>N,N</u> -dimetilcarbamoilo, <u>N</u> -etil- <u>N</u> -metilcarbamoilo y <u>N,N</u> -dietilcarbamoilo;
para (2-6C)alcanoilo:	acetilo y propionilo;
para (2-6C)alcanoiloxi:	acetoxi y propioniloxi;
para (2-6C)alcanoilamino:	acetamido y propionamido;
para <u>N</u> -(1-6C)alquil-(2-6C)alcanoilamino:	<u>N</u> -metilacetamido y <u>N</u> -metilpropionamido;
para amino(2-6C)alcanoilo:	aminoacetilo y 2-aminopropionilo;
para <u>N</u> -(1-6C)alquilamino(2-6C)alcanoilo:	<u>N</u> -metilaminoacetilo y 2-(<u>N</u> -metilaminopropionilo);
para <u>N,N</u> -di-[(1-6C)alquil]amino(2-6C)alcanoilo:	<u>N,N</u> -di-metilaminoacetilo;
para <u>N</u> -(1-6C)alquilsulfamoilo:	<u>N</u> -metilsulfamoilo y <u>N</u> -etilsulfamoilo;
para <u>N,N</u> -di-[(1-6C)alquil]sulfamoilo:	<u>N,N</u> -dimetilsulfamoilo;

para (1-6C)alcanosulfonilamino:

metanosulfonilamino y
etanosulfonilamino;

para N-(1-6C)alquil-(1-
6C)alcanosulfonilamino:

N-metilmetanosulfonilamino y N-
metiletanosulfonilamino;

para (3-6C)alquenoilamino:

acrilamido, metacrilamido y
crotonamido;

para N-(1-6C)alquil-(3-
6C)alquenoilamino:

N-metilacrilamido y N-
metilcrotonamido;

para (3-6C)alquinoilamino:

propiolamido;

para N-(1-6C)alquil-(3-
6C)alquinoilamino:

N-metilpropiolamido;

para amino-(1-6C)alquilo:

aminometilo, 2-aminoetilo, 1-
aminoetilo y 3-aminopropilo;

para (1-6C)alquilamino-(1-6C)alquilo:

metilaminometilo, etilaminometilo,
1-metilaminoetilo, 2-metilaminoetilo,
2-etilaminoetilo y 3-
metilaminopropilo;

para di-[(1-6C)alquil]amino-(1-
6C)alquilo:

dimetilaminometilo,
dietilaminometilo, 1-
dimetilaminoetilo, 2-
dimetilaminoetilo y 3-
dimetilaminopropilo;

para halógeno-(1-6C)alquilo:

clorometilo, 2-cloroetilo, 1-cloroetilo
y 3-cloropropilo;

para hidroxí- (1 -6C)alquilo:

hidroximetilo, 2-hidroxietilo, 1 -
hidroxietilo y 3-hidroxipropilo;

para (1-6C)alcoxi-(1-6C)alquilo:

metoximetilo, etoximetilo, 1-
metoxietilo, 2-metoxietilo, 2-
etoxietilo y 3-metoxipropilo;

para ciano-(1-6C)alquilo:

cianometilo, 2-cianoetilo, 1-
cianoetilo y 3-cianopropilo;

para carboxi-(1-6C)alquilo:	carboximetilo, 2-carboxietilo, 1-carboxietilo y 3-carboxipropilo;
para (1-6C)alquiltio-(1-6C)alquilo:	metiltiometilo, etiltiometilo, 2-metiltioetilo, 1-metiltioetilo y 3-metiltiopropilo;
para (1-6C)alquilsulfinil-(1-6C)alquilo:	metilsulfinilmetilo, etilsulfinilmetilo, 2-metilsulfiniletilo, 1-metilsulfiniletilo y 3-metilsulfinilpropilo;
para (1-6C)alquilsulfonil-(1-6C)alquilo:	metilsulfonilmetilo, etilsulfonilmetilo, 2-metilsulfoniletilo, 1-metilsulfoniletilo y 3-metilsulfonilpropilo;
para (2-6C)alcanoilamino-(1-6C)alquilo:	acetamidometilo, propionamidometilo y 2-acetamidoetilo;
para (1-6C)alcoxycarbonil-(1-6C)alquilo:	metoxycarbonilmetilo, 2-metoxycarboniletilo y 2-etoxycarboniletilo;
para (1-6C)alcoxycarbonilamino-(1-6C)alquilo:	metoxycarbonilaminometilo, etoxycarbonilaminometilo, <u>tert</u> -butoxycarbonilaminometilo y 2-metoxycarbonilaminoetilo;
para carbamoil-(1-6C)alquilo:	carbamoilmetilo, 1-carbamoiletilo, 2-carbamoiletilo y 3-carbamoilpropilo;
para (2-6C)alcanoil-(1-6C)alquilo:	acetilmetilo y 2-acetiletilo;
para <u>N</u> -(1-6C)alquilcarbamoil-(1-6C)alquilo:	<u>N</u> -metilcarbamoilmetilo, <u>N</u> -etilcarbamoilmetilo, <u>N</u> -propilcarbamoilmetilo, 1-(<u>N</u> -metilcarbamoil)etilo, 1-(<u>N</u> -etilcarbamoil)etilo, 2-(<u>N</u> -metilcarbamoil)etilo, 2-(<u>N</u> -etilcarbamoil)etilo y 3-(<u>N</u> -metilcarbamoil)propilo; y

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para N,N-di[(1-6C)alquil]carbamoil-(1-6C)alquilo:

N,N-dimetilcarbamoilmetilo, N,N-dietilcarbamoilmetilo, 2-(N,N-dimetilcarbamoil)etilo, y 3-(N,N-dimetilcarbamoil)propilo.

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Un valor apropiado para $(R^1)_m$ cuando éste es un grupo (1-3C)alquilenodioxo es, por ejemplo, metilenodioxo o etilenodioxo y los átomos de oxígeno de los mismos ocupan posiciones de anillo adyacentes.

Cuando en esta especificación se hace referencia a un grupo (1-4C)alquilo hay que entender que tales grupos se refieren a grupos alquilo que contienen hasta 4 átomos de carbono. Un experto entenderá que ejemplos representativos de tales grupos son los listados arriba bajo (1-6C)alquilo que contienen hasta 4 átomos de carbono, tales como metilo, etilo, propilo y butilo. Análogamente, la referencia a un grupo (1-3C)alquilo alude a grupos alquilo que contienen hasta 3 átomos de carbono tales como metilo, etilo y propilo. Una convención similar se adopta para los otros grupos enumerados arriba tales como (1-4C)alcoxi, (2-4C)alquenoilo, (2-4C)alquinoilo y (2-4C)alcanoilo.

Cuando, como se define arriba en el texto, un grupo R^1 forma un grupo de la fórmula Q^3-X^1 y, por ejemplo, X^1 es un grupo enlazante $OC(R^4)_2$, es el átomo de carbono, no el átomo de oxígeno, del grupo enlazante $OC(R^4)_2$ el cual se une al anillo de quinazolina y el átomo de oxígeno se une al grupo Q^3 . Análogamente, cuando, por ejemplo un grupo CH_3 en un sustituyente R^1 lleva un grupo de la fórmula $-X^3-Q^5$ y, por ejemplo, X^3 es un grupo enlazante $C(R^7)_2O$, es el átomo de carbono, no el átomo de oxígeno, del grupo enlazante $C(R^7)_2O$ el cual se une al grupo CH_3 y el átomo de oxígeno se enlaza al grupo Q^5 . Una convención similar se aplica a la unión de los grupos de las Fórmulas Q^4-X^2 y $-X^7-Q^7$.

Como se define arriba en el texto, átomos de carbono adyacentes en cualquier cadena (2-6C)alquilo en un sustituyente R^1 puede separarse opcionalmente por la inserción en la cadena de un grupo tal como O, $CON(R^5)$, $N(R^5)$ ó $C\equiv C$. Por ejemplo, la inserción de un grupo $C\equiv C$ en la cadena etileno en un grupo 2-morfolinoetoxi da lugar a un grupo 4-

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morfolinobut-2-iniloxi y, por ejemplo, la inserción de un grupo CONH en la cadena etileno en un grupo 3-metoxipropoxi da lugar a, por ejemplo, un grupo 2-(2-metoxiacetamido)etoxi. Hay que entender que el término cadena (2-6C)alquileo se refiere a cualquier grupo CH_2CH_2 en R^1 e incluye, por ejemplo cadenas alquileo en un grupo (1-6C)alquilo, (1-6C)alcoxi, (2-8C)alquenilo, (2-8C)alqueniloxi, (2-8C)alquinil y (2-8C)alquiniloxi. Por ejemplo la inserción de un grupo $\text{N}(\text{CH}_3)$ entre los átomos de carbono tercero y cuarto en un grupo hex-5-eniloxi en R^1 da lugar a un grupo 3-(N-metil-N-alilamino)propoxi.

Cuando, como se define arriba en el texto, cualquier grupo $\text{CH}_2=\text{CH}-$ o $\text{HC}\equiv\text{C}-$ en un sustituyente R^1 lleva opcionalmente en la posición terminal $\text{CH}_2=$ ó $\text{HC}\equiv$ un sustituyente tal como un grupo de la fórmula Q^4-X^2 en donde X^2 es, por ejemplo, NHCO y Q^4 es un grupo heterociclil-(1-6C)alquilo, sustituyentes R^1 apropiados así formados incluyen, por ejemplo, grupos N-[heterociclil-(1-6C)alquil]carbamoilvinilo tales como grupos N-(2-pirrolidin-1-iletíl)carbamoilvinilo o N-[heterociclil-(1-6C)alquil]carbamoiletinilo tales como N-(2-pirrolidin-1-iletíl)carbamoiletinilo.

Cuando, como se define arriba en el texto, cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo, hay apropiadamente 1 ó 2 sustituyentes halógeno o (1-6C)alquilo presentes en cada dicho grupo CH_2 y hay apropiadamente 1, 2 ó 3 sustituyentes semejantes presentes en cada uno de dichos grupos CH_3 .

Cuando, como se define arriba en el texto, cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente como se define arriba en el texto, sustituyentes R^1 apropiados así formados incluyen, por ejemplo, grupos heterociclil-(1-6C)alcoxi hidroxi-sustituidos tales como grupos 2-hidroxi-3-piperidinopropoxi y 2-hidroxi-3-morfolinopropoxi, grupos amino-(2-6C)alcoxi hidroxi-sustituidos tales como grupos 3-amino-2-hidroxipropoxi, hidroxi-sustituido (1-6C)alquilamino-(2-6C)alcoxi tales como grupos 2-

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hidroxi-3-metilaminopropoxi, hidroxi-sustituido di-[(1-6C)alquil]amino-(2-6C)alcoxi tales como grupos 3-dimetilamino-2-hidroxipropoxi, heterociclil-(1-6C)alquilamino hidroxi-sustituidos tales como grupos 2-hidroxi-3-piperidinopropilamino y 2-hidroxi-3-morfolinopropilamino, amino-(2-6C)alquilamino hidroxi-sustituidos tales como grupos 3-amino-2-hidroxipropilamino, hidroxi-sustituido (1-6C)alquilamino-(2-6C)alquilamino tales como grupos 2-hidroxi-3-metilaminopropilamino, hidroxi-sustituido di-[(1-6C)alquil]amino-(2-6C)alquilamino tales como grupos 3-dimetilamino-2-hidroxipropilamino, (1-6C)alcoxi hidroxi-sustituido tales como grupos 2-hidroxietoxi, (1-6C)alcoxi (1-6C)alcoxi-sustituidos tales como grupos 2-metoxietoxi y 3-etoxipropoxi, (1-6C)alcoxi(1-6C)alquilsulfonil-sustituidos tales como grupos 2-metilsulfoniletoxi y heterociclil-sustituido (1-6C)alquilamino-(1-6C)alquilo tales como 2-morfolinoetilaminometilo, 2-piperazin-1-iletilaminometilo y 3-morfolinopropilaminometilo.

Consideraciones similares se aplican a las uniones y sustituciones en el grupo -Z-Q¹.

Hay que entender que cuando, como se define arriba en el texto, cualquier grupo CH₂ ó CH₃ en un sustituyente R¹ o un grupo Q¹-Z- lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente como se define arriba en el texto, el sustituyente opcional puede estar presente en cualquier grupo CH₂ ó CH₃ en un sustituyente R¹ o un grupo Q¹-Z-, incluidos aquellos en los sustituyentes definidos más arriba en el texto que pueden estar presentes en un grupo arilo, heteroarilo o heterociclilo en R¹ o Q¹-Z-. Por ejemplo, si Q¹ es un grupo 1-(1-6C)alquil-piperidin-4-ilo, el grupo (1-6C)alquilo puede sustituirse opcionalmente por, por ejemplo un grupo (2-6C)alcanoilo para producir un grupo 1-((2-6C)alcanoil-(1-6C)alquil)-piperidin-4-ilo tal como 1-(acetilmetil)piperidin-4-ilo o 1-(2-acetiletil)piperidin-4-ilo. Otros grupos apropiados que pueden formarse de esta manera por Q¹ incluyen grupos heterociclilo (1-6C)alcoxycarbonil-(1-6C)alquilo sustituidos, tales como 1-(metoxycarbonilmetil)piperidin-4-ilo o 1-(2-metoxycarboniletil)piperidin-4-ilo, grupo heterociclilo carbamoil-(1-



6C)alquilo sustituidos tales como grupos heterociclilo 1-(carbamoilmetil)piperidin-4-ilo, o (1-6C)alcoxi-(1-6C)alquilo sustituidos, tales como 1-(2-metoxietil)piperidin-4-ilo. Análogamente cuando R^1 es un grupo arilo (1-6C)alquilo sustituido, o heteroarilo, el grupo (1-6C)alquilo puede sustituirse opcionalmente por uno de los sustituyentes definidos más arriba en el texto que pueden estar presentes en un grupo CH_2 ó CH_3 . Por ejemplo si R^1 es un grupo heteroarilo sustituido por (1-6C)alquilamino-(1-6C)alquilo; el grupo terminal CH_3 del sustituyente alquilo puede sustituirse además por, por ejemplo, un grupo (1-6C)alquilsulfonilo. A modo de ejemplo, si R^1 es un grupo 2-(etilaminometil)-5-furilo, el grupo etilo puede sustituirse opcionalmente por un grupo metilsulfonilo para producir un grupo 2-(2-metilsulfoniletilaminometil)-5-furilo.

Consideraciones similares se aplican a sustituyentes que están opcionalmente presentes en el grupo terminal de un grupo $CH_2=CH-$ ó $HC\equiv C-$ en un sustituyente R^1 o un grupo Q^1-Z- .

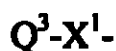
Cuando, como se define arriba en el texto, G^3 y G^4 juntos forman, por ejemplo, un grupo de fórmula $-O-CH=CH-$, es el átomo de oxígeno, no el átomo de carbono, el cual se une a la posición para G^3 del anillo fenilo de fórmula Ia y el átomo de carbono se une a la posición meta G^4 adyacente del anillo fenilo de fórmula Ia.

Una sal apropiada farmacéuticamente aceptable de un compuesto de la Fórmula I es, por ejemplo, una sal de adición de ácido de un compuesto de la Fórmula I, por ejemplo una sal de adición de ácido con un ácido orgánico o inorgánico tal como ácido clorhídrico, bromhídrico, sulfúrico, trifluoroacético, cítrico o maleico; o, por ejemplo, una sal de un compuesto de la Fórmula I que es suficientemente ácido, por ejemplo una sal de un metal alcalino o alcalinotérreo tal como una sal de calcio o magnesio, o una sal de amonio, o una sal con una orgánica tal como metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

Compuestos novedosos particulares de la invención incluyen, por ejemplo, derivados de quinazolina de la Fórmula I, o sales

farmacéuticamente aceptables de los mismos, en donde, a menos que se indique lo contrario, cada uno de m , R^1 , R^2 , R^3 , Z , L , Q^1 y Q^2 tiene cualquiera de los significados definidos más arriba en el texto o en los párrafos (a) a (www) que siguen:

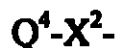
(a) cada grupo R^1 , que puede ser el mismo o diferente, se selecciona de halógeno, trifluorometilo, hidroxilo, amino, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino, $\underline{N}$ -(1-6C)alquilcarbamoilo, $\underline{N,N}$ -di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilamino, $\underline{N}$ -(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, $\underline{N}$ -(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino y $\underline{N}$ -(1-6C)alquil-(3-6C)alquinoilamino, o de un grupo de la fórmula:



en donde X^1 es un enlace directo o se selecciona de O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ y $OC(R^4)_2$ en donde R^4 es hidrógeno o (1-6C)alquilo, y Q^3 es arilo, aril-(1-6C)alquilo, cicloalquil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, $CH=CH$ y $C\equiv C$ en donde R^5 es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo $CH_2=CH-$ ó $HC\equiv C-$ en un sustituyente R^1 lleva opcionalmente en la posición terminal $CH_2=$ ó $HC\equiv$ un sustituyente seleccionado de carbamoilo, $\underline{N}$ -(1-6C)alquilcarbamoilo, $\underline{N,N}$ -di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquilo o de un grupo de la fórmula:

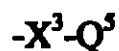


en donde X^2 es un enlace directo o es CO o $N(R^6)CO$, en donde R^6 es hidrógeno o (1-6C)alquilo, y Q^4 es heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva

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opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, (1-6C)alcoxi, (1-6C)alquilsulfonilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O, $\text{N}(\text{R}^7)$, $\text{CON}(\text{R}^7)$, $\text{N}(\text{R}^7)\text{CO}$ y $\text{C}(\text{R}^7)_2\text{O}$, en donde R^7 es hidrógeno o (1-6C)alquilo, y Q^5 es heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, hidroxilo, amino, carbamoilo, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino, N-(1-6C)alquilcarbamoilo y N,N-di-[(1-6C)alquil]carbamoilo, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X^4 es un enlace directo o se selecciona de O y $\text{N}(\text{R}^9)$, en donde R^9 es hidrógeno o (1-6C)alquilo, y R^8 es hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo o (1-6C)alcoxycarbonilamino-(1-6C)alquilo, y de un grupo de la fórmula:

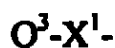


en donde X^5 es un enlace directo o se selecciona de O y $\text{N}(\text{R}^{10})$, en donde R^{10} es hidrógeno o (1-6C)alquilo, y Q^6 es heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(b) cada grupo R^1 , que puede ser el mismo o diferente, se selecciona de fluoro, cloro, trifluorometilo, hidroxilo, amino, carbamoilo, metilo, etilo, propilo, vinilo, etinilo, metoxi, etoxi, propoxi, metilamino, etilamino,

propilamino, dimetilamino, dietilamino, dipropilamino, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido y propiolamido, o de un grupo de la fórmula:

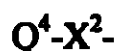


en donde X^1 es un enlace directo o se selecciona de O, NH, CONH, NHCO y OCH_2 y Q^3 es fenilo, bencilo, ciclopropilmetilo, 2- ó 3-tienilo, 2- ó 3-tienilmetilo, 2-(2- ó 3-tienil)etilo, tetrahidrotien-2-ilo, tetrahidrotien-3-ilo, tetrahidrotien-2-ilmetilo, 2-(tetrahidrotien-2-il)etilo, tetrahidrotien-3-ilmetilo, 2-(tetrahidrotien-3-il)etilo, 2- ó 3-furilo, furfurilo, 2-(2-furil)etilo, 3-furilmetilo, 2-(3-furil)etilo, tetrahidrofuran-2-ilo, tetrahidrofuran-3-ilo, tetrahidrofurfurilo, 2-(tetrahidrofuran-2-il)etilo, tetrahidrofuran-3-ilmetilo, 2-(tetrahidrofuran-3-il)etilo, 1-imidazolilo, 1,2,3-triazol-1-ilo, 2-, 3- ó 4-piridilo, 2-imidazol-1-iletilo, 3-imidazol-1-ilpropilo, 2-(1,2,3-triazolil)etilo, 3-(1,2,3-triazolil)propilo, 2-, 3- ó 4-piridilmetilo, 2-(2-, 3- ó 4-piridil)etilo, 3-(2-, 3- ó 4-piridil)propilo, 1-, 2- ó 3-pirrolidinilo, morfolino, 1,1-dioxotetrahidro-4H-1,4-tiazin-4-ilo, piperidino, piperidin-3-ilo, piperidin-4-ilo, 1-, 3- ó 4-homopiperidinilo, piperazin-1-ilo, homopiperazin-1-ilo, 1-, 2- ó 3-pirrolidinilmetilo, morfolinometilo, piperidinometilo, 3- ó 4-piperidinilmetilo, 1-, 3- ó 4-homopiperidinilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-2-ilpropilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-1-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etilo, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperidin-3-iletilo, 2-piperidin-4-iletilo, 2-homopiperidin-1-iletilo, 3-homopiperidin-1-ilpropilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo, 2-homopiperazin-1-iletilo o 3-homopiperazin-1-ilpropilo, y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, $N(CH_3)$, CONH, NHCO, $CH=CH$ y $C\equiv C$,

y en donde cualquier grupo $CH_2=CH-$ o $HC\equiv C-$ en un sustituyente R^1 lleva opcionalmente en la posición terminal $CH_2=$ ó $HC\equiv$ un sustituyente seleccionado de carbamoilo, N-metilcarbamoilo, N-



etilcarbamoilo, N-propilcarbamoilo, N,N-dimetilcarbamoilo, aminometilo, 2-aminoetilo, 3-aminopropilo, 4-aminobutilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 4-metilaminobutilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo o 4-dimetilaminobutilo, o de un grupo de la fórmula:

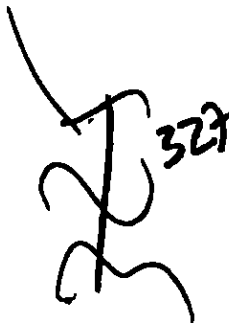


en donde X^2 es un enlace directo o es CO, NHCO o $N(CH_3)CO$ y Q^4 es 2-, 3- ó 4-piridilo, 2-, 3- ó 4-piridilmetilo, 2-piridiletilo, pirrolidin-1-ilo, pirrolidin-2-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 4-pirrolidin-1-ilbutilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, 4-morfolinobutilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, 4-piperidinobutilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo ó 4-piperazin-1-ilbutilo,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O, NH, $N(CH_3)$, CONH, NHCO y CH_2O y Q^5 es 2- ó 3-furilo, furfurilo, 2-(2-furil)etilo, 3-furilmetilo, (3-furil)etilo, tetrahydrofuran-2-ilo, tetrahydrofuran-3-ilo, tetrahydrofurfurilo, 2-(tetrahydrofuran-2-il)etilo, tetrahydrofuran-3-ilmetilo, 2-(tetrahydrofuran-3-il)etil 2-, 3- ó 4-piridilo, 2-, 3- ó 4-piridilmetilo, pirrolidin-1-ilo, pirrolidin-2-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, 2-piperazin-1-iletilo o 3-piperazin-1-

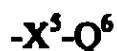


ilpropilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1,2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, carbamilo, metilo, etilo, metilamino, dimetilamino y metoxi, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



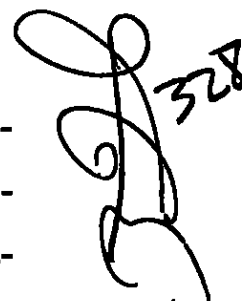
en donde X^4 es un enlace directo o se selecciona de O y NH, y R^8 es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, aminometilo, 2-aminoetilo, 3-aminopropilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-etilaminoetilo, 3-etilaminopropilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, acetamidometilo, metoxycarbonilaminometilo, etoxycarbonilaminometilo o tert-butoxycarbonilaminometilo, y de un grupo de la fórmula:



en donde X^5 es un enlace directo o se selecciona de O y NH, y Q^6 es pirrolidin-2-ilo, pirrolidin-3-ilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, tetrahidrofuran-2-ilo, tetrahidrofuran-3-ilo, tetrahidrofurfurilo, 2-(tetrahidrofuran-2-il)etilo, tetrahidrofuran-3-ilmetilo, 2-(tetrahidrofuran-3-il)etilo, piperidin-4-ilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo o 3-piperazin-1-ilpropilo, cada de los cuales lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(c) m es 1 ó 2 y los grupos R^1 , que pueden ser los mismos o diferentes, están localizados en las posiciones 6 y/o 7 y se seleccionan de hidroxilo, amino, metilo, etilo, propilo, vinilo, etinilo, metoxi, etoxi, propoxi, metilamino, etilamino, dimetilamino, dietilamino, acetamido,



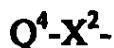
propionamido, benciloxi, ciclopropilmetoxi, 2-ciclopropiletoxi, 2-imidazol-1-iletoxi, 3-imidazol-1-ilpropoxi, 2-(1,2,3-triazol-1-il)etoxi, 3-(1,2,3-triazol-1-il)propoxi, pirid-2-ilmetoxi, pirid-3-ilmetoxi, pirid-4-ilmetoxi, 2-pirid-2-iletoxi, 2-pirid-3-iletoxi, 2-pirid-4-iletoxi, 3-pirid-2-ilpropoxi, 3-pirid-3-ilpropoxi, 3-pirid-4-ilpropoxi, tetrahidrofurfuriloxi, 2-(tetrahidrofuran-2-il)etoxi, 3-(tetrahidrofuran-2-il)propoxi, 2-(tetrahidrofuran-3-il)etoxi, 3-(tetrahidrofuran-3-il)propoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi, 3-homopiperazin-1-ilpropoxi, 2-pirrolidin-1-iletilamino, 3-pirrolidin-1-ilpropilamino, pirrolidin-3-ilamino, pirrolidin-2-ilmetilamino, 2-pirrolidin-2-iletilamino, 3-pirrolidin-2-ilpropilamino, 2-morfolinoetilamino, 3-morfolinopropilamino, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etilamino, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propilamino, piperidin-4-ilamino, piperidin-3-ilmetilamino, 2-piperidin-3-iletilamino, piperidin-4-ilmetilamino, 2-piperidin-4-iletilamino, 2-homopiperidin-1-iletilamino, 3-homopiperidin-1-ilpropilamino, 2-piperazin-1-iletilamino, 3-piperazin-1-ilpropilamino, 2-homopiperazin-1-iletilamino, 3-homopiperazin-1-ilpropilamino, pirrolidin-1-ilo, morfolino, piperidino, piperazin-1-ilo, 2-furilo, 3-furilo, tetrahidrofuran-2-ilo y tetrahidrofuran-2-ilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(CH₃), CH=CH y C≡C,

y cuando R¹ es un grupo vinilo o etinilo, el sustituyente R¹ lleva opcionalmente en la posición terminal CH₂= ó HC≡ un sustituyente



seleccionado de N-(2-dimetilaminoetil)carbamoilo, N-(3-dimetilaminopropil)carbamoilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 4-metilaminobutilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo y 4-dimetilaminobutilo, o de un grupo de la fórmula:



en donde X^2 es un enlace directo o es NHCO o $N(CH_3)CO$ y Q^4 es imidazolilmetilo, 2-imidazoliletilo, 3-imidazolilpropilo, piridilmetilo, 2-piridiletilo, 3-piridilpropilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 4-pirrolidin-1-ilbutilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, 4-morfolinobutilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, 4-piperidinobutilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo ó 4-piperazin-1-ilbutilo,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

y en donde cualquier grupo fenilo, piridilo, furilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, metilamino, etilamino, dimetilamino, dietilamino, carbamoilo, metilo, etilo, n-propilo, isopropilo y metoxi, y cualquier grupo piperidin-3-ilmetilo, piperidin-4-ilmetilo, 2-piperazin-1-iletilamino, 3-piperazin-1-ilpropilamino, o piperazin-1-ilo en un sustituyente R^1 es opcionalmente N-sustituido con 2-metoxietilo, 3-metoxipropilo, 2-aminoetilo, 3-aminopropilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperazin-1-iletilo ó 3-piperazin-1-

ilpropilo, los últimos 8 de los cuales sustituyentes lleva cada uno opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes oxo;

(d) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de metilo, etilo, propilo, butilo, pentilo, vinilo, etinilo, metoxi, etoxi, propoxi, butoxi, pentoxi, amino, metilamino, etilamino, propilamino, dimetilamino, dietilamino, N-propil-N-metilamino, carbamoilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido, propiolamido, pirrolidin-1-ilo, piperidino, homopiperidin-1-ilo, morfolino, 1,4-oxazepan-4-ilo, tiamorfolino, piperazin-1-ilo y homopiperazin-1-ilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(CH₃), CO, CONH y NHCO,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R¹ lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, etilsulfonilo, metilamino, etilamino, dimetilamino y dimetilamino, o de un grupo de la fórmula:



en donde X³ es un enlace directo o se selecciona de O, NH, N(CH₃), CO, NHCO y CONH, y Q⁵ es fenilo, bencilo, 2-feniletilo, 2-furilo, furfurilo, 2-(2-furil)etilo, 3-furilo, 2-(3-furil)etilo, 2-piridilo, 2-piridilmetilo, 2-(2-piridil)etilo, 3-piridilo, 3-piridilmetilo, 2-(3-piridil)etilo, 4-piridilo, 4-piridilmetilo, 2-(4-piridil)etilo, 2-pirimidinilo, 2-pirimidinilmetilo, 2-(2-pirimidinil)etilo, 4-pirimidinilo, 4-pirimidinilmetilo, 2-(4-pirimidinil)etilo, 5-pirimidinilo, 5-pirimidinilmetilo, 2-(5-pirimidinil)etilo, tetrahydrofuran-2-ilo, tetrahydrofurfurilo, 2-tetrahydrofuran-2-iletilo, tetrahydrofuran-3-ilo, tetrahydrofuran-3-ilmetilo, 2-tetrahydrofuran-3-iletilo, pirrolidin-1-ilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, pirrolidin-2-ilo, pirrolidin-2-

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ilmetilo, 2-pirrolidin-2-iletilo, pirrolidin-3-ilo, pirrolidin-3-ilmetilo, 2-pirrolidin-3-iletilo, morfolino, morfolinometilo, 2-morfolinoetilo, piperidino, piperidinometilo, 2-piperidinoetilo, piperidin-3-ilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, homopiperidin-1-ilo, homopiperidin-1-ilmetilo, 2-homopiperidin-1-iletilo, piperazin-1-ilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, homopiperazin-1-ilo, homopiperazin-1-ilmetilo y 2-homopiperazin-1-iletilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en R¹ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, carbamoilo, metilo, etilo, metilamino, dimetilamino y metoxi,

o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X⁴ es un enlace directo o se selecciona de O y NH y R⁸ es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, aminometilo, 2-aminoetilo, 3-aminopropilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-etilaminoetilo, 3-etilaminopropilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, acetamidometilo, metoxycarbonilaminometilo, etoxycarbonilaminometilo o tert-butoxycarbonilaminometilo, y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes oxo;

(e) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de trifluorometilo, hidroxilo, amino, carbamoilo, metilo, etilo, propilo, butilo, pentilo, vinilo, etinilo, metoxi, etoxi, propoxi, butoxi, pentoxi, metilamino, etilamino, propilamino, dimetilamino, dietilamino, propilmetilamino, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido, propiolamido, pirrolidin-lilo, piperidino, homopiperidin-1-ilo, morfolino, tiamorfolino, piperazin-1-ilo y homopiperazin-1-ilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-



6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(CH₃), CO, CONH y NHCO,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxí, amino, metoxi, metilsulfonilo, metilamino, y dimetilamino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O, NH y N(CH₃) y Q^3 se selecciona de pirrolidin-1-ilo, pirrolidin-2-ilo, pirrolidin-3-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-1-ilo, piperazin-1-il homopiperazin-1-ilo, fenilo, (2-, 3- ó 4-)piridilo y (2-, 4- ó 5-)pirimidinilo,

y en donde cualquier grupo fenilo, piridilo, pirimidinilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxí, metilo, etilo, n-propilo, isopropilo, metoxi, etoxi, 2-metoxietoxi, 2-hidroxietoxi, 3-hidroxipropoxi, 3-metoxipropoxi, aminometoxi, 2-aminoetoxi, 3-aminopropoxi, metilaminometoxi, 2-metilaminoetoxi, 2-etilaminoetoxi, dimetilaminometoxi, 2-dimetilaminoetoxi, amino, metilamino, dimetilamino, y en donde cualquier fracción pirrolidinilo, piperidinilo, piperazinilo, homopiperidinilo u homopiperazinilo en R^1 se sustituye opcionalmente además, en un átomo de nitrógeno disponible, con un sustituyente seleccionado de tetrahidrofurfurilo, tetrahidrofuran-3-ilmetilo, 1-metilpiperidin-4-il 1-etilpiperidin-4-ilo, 1-metilpiperidin-3-il 1-etilpiperidin-3-il y 2-morfolinoetilo, y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(f) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de hidroxí, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, metilamino, etilamino, propilamino, dimetilamino, dietilamino, N-

propil-N-metilamino, acetamido, propionamido, benciloxi, pirrolidin-1-ilo, 2-imidazol-1-iletoxi, 2-(1,2,4-triazol-1-il)etoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi o 3-homopiperazin-1-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(CH₃), CH=CH y C≡C,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R¹ lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

y en donde cualquier grupo fenilo o heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, metilo, etilo, metoxi, metilamino y dimetilamino,

y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes oxo;

(g) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de hidroxilo, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

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y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH y $N(CH_3)$,

y en donde cualquier grupo terminal CH_3 en una cadena (1-6C)alcoxi en un sustituyente R^1 lleva opcionalmente en el grupo terminal CH_3 un sustituyente seleccionado de hidroxilo, amino y N-(1-metilpirrolidin-3-il)-N-metilamino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R^1 lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en un sustituyente R^1 lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahidrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo;

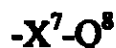
- (h) m es 0;
- (i) m es 1 y R^1 se localiza en la posición 7;
- (j) R^3 es hidrógeno;
- (k) L es un enlace directo o $CH(R^{22})$, en donde R^{22} es hidrógeno, metilo o etilo;
- (l) Z es un enlace directo o se selecciona de O, S, SO, SO_2 , $N(R^{11})$ y CO;
- (m) Z se selecciona de $CON(R^{11})$, $N(R^{11})CO$, $SO_2N(R^{11})$, $N(R^{11})SO_2$, $OC(R^{11})_2$, $SC(R^{11})_2$ y $N(R^{11})C(R^{11})_2$, en donde R^{11} es hidrógeno o (1-6C)alquilo;
- (n) Z es O;
- (o) Z es un enlace directo o se selecciona de O, S, SO, SO_2 , $N(R^{11})$ y CO en donde R^{11} es hidrógeno o (1-6C)alquilo, y Q^1 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno en el grupo Q^1 -Z- se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, $N(R^{12})$, $CON(R^{12})$, $N(R^{12})CO$,

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$\text{CH}=\text{CH}$ y $\text{C}\equiv\text{C}$ en donde R^{12} es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo CH_2 ó CH_3 en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxí, amino, (1-6C)alcoxi, (1-6C)alquilsulfonilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino, o de un grupo de la fórmula:



en donde X^7 es un enlace directo o se selecciona de O, $\text{N}(\text{R}^{14})$, $\text{CON}(\text{R}^{14})$, $\text{N}(\text{R}^{14})\text{CO}$ y $\text{C}(\text{R}^{14})_2\text{O}$, en donde R^{14} es hidrógeno o (1-6C)alquilo, y Q^8 es heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, hidroxí, amino, carbamoilo, (1-6C)alquilo, (1-6C)alcoxi, (1-4C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo y N,N-di-[(1-6C)alquil]carbamoilo, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X^8 es un enlace directo o se selecciona de O y $\text{N}(\text{R}^{16})$, en donde R^{16} es hidrógeno o (1-6C)alquilo, y R^{15} es hidroxí-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo, (1-6C)alcoxycarbonilamino-(1-6C)alquilo o un grupo de la fórmula:



en donde X^9 es un enlace directo o se selecciona de O y $\text{N}(\text{R}^{17})$, en donde R^{17} es hidrógeno o (1-6C)alquilo, y Q^9 es heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente 1 ó 2 sustituyentes oxo;

(p) el grupo $\text{Q}^1\text{-Z-}$ se selecciona de ciclopropiloxi, ciclobutiloxi,

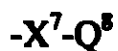
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ciclopentiloxi, ciclohexiloxi, cicloheptiloxi, ciclopropilmetoxi, ciclobutilmetoxi, ciclopentilmetoxi, ciclohexilmetoxi y cicloheptilmetoxi,

o Z es un enlace directo o se selecciona de O, S, SO, SO₂ y NH y Q¹ es fenilo, bencilo, 2-tienilo, 1-imidazolilo, 1,2,3-triazol-1-ilo, 1,2,4-triazol-1-ilo, 2-, 3- ó 4-piridilo, 2-imidazol-1-iletilo, 3-imidazol-1-ilpropilo, 2-(1,2,3-triazol-1-il)etilo, 2-(1,2,4-triazol-1-il)etilo, 3-(1,2,3-triazol-1-il)propilo, 3-(1,2,4-triazol-1-il)propilo, 2-, 3- ó 4-piridilmetilo, 2-(2-, 3- ó 4-piridil)etilo, 3-(2-, 3- ó 4-piridil)propilo, oxetan-3-ilo, tetrahydrofuran-3-ilo, 3- ó 4-tetrahidropiraniilo, 3- ó 4-oxepaniilo, 1-, 2- ó 3-pirrolidinilo, morfolino, 1,1-dioxotetrahidro-4H-1,4-tiazin-4-ilo, piperidino, piperidin-3-ilo, piperidin-4-ilo, 1-, 3- ó 4-homopiperidinilo, piperazin-1-ilo, homopiperazin-1-ilo, azetidín-3-ilo, tetrahidrotien-3-ilo, 1,1-dioxotetrahidrotien-3-ilo, 1-oxotetrahidrotien-3-ilo, tetrahidrotiopiran-3-ilo, tetrahidrotiopiran-4-ilo, 1-oxotetrahidrotiopiran-3-ilo, 1,1-dioxotetrahidrotiopiran-3-ilo, 1-oxotetrahidrotiopiran-4-ilo, 1,1-dioxotetrahidrotiopiran-4-ilo, 1-, 2- ó 3-pirrolidinilmetilo, morfolinometilo, piperidinometilo, 3- ó 4-piperidinilmetilo, 1-, 3- ó 4-homopiperidinilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etilo, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperidin-3-iletilo, 2-piperidin-4-iletilo, 2-homopiperidin-1-iletilo, 3-homopiperidin-1-ilpropilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo, 2-homopiperazin-1-iletíl o 3-homopiperazin-1-ilpropilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en el grupo Q¹-Z- se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, CONH, NHCO, CH=CH y OC,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q¹-Z- lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxí, amino, metoxi, metilsulfonilo, metilamino y dimetilamino, o de un grupo de la fórmula:

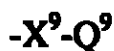


en donde X^7 es un enlace directo o se selecciona de O, NH, CONH, NHCO y CH_2O y Q^8 es piridilo, piridilmetilo, pirrolidin-1-ilo, pirrolidin-2-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, 2-piperazin-1-iletíl o 3 -piperazin-1-ilpropilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en el grupo Q^1-Z lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxí, amino, carbamoilo, metilo, etilo y metoxi, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X^8 es un enlace directo o se selecciona de O y NH y R^{15} es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, aminometilo, 2-aminoetilo, 3-aminopropilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-etilaminoetilo, 3-etilaminopropilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, acetamidometilo, metoxicarbonilaminometilo, etoxicarbonilaminometil o tert-butoxicarbonilaminometilo, y de un grupo de la fórmula:



en donde X^9 es un enlace directo o se selecciona de O y NH y Q^9 es pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo o 3-piperazin-1-ilpropilo, cada uno de los cuales lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo en el grupo Q^1-Z lleva opcionalmente 1 ó 2 sustituyentes oxo;

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(q) el grupo Q¹-Z- se selecciona de ciclobutiloxi, ciclopentiloxi, ciclohexiloxi, cicloheptiloxi, fenoxi, feniltio, anilino, benciloxi, ciclopropilmetoxi, tetrahidrofuran-3-iloxi, tetrahidrofurfuriloxi, 3- ó 4-tetrahidropiraniloxi, 2-tetrahidropiran-4-iletoxi, 2-tetrahidropiran-3-iletoxi, 3-tetrahidropiran-4-ilpropoxi, 3-tetrahidropiran-3-ilpropoxi, tetrahidrotiopiran-3-iloxi, 2-tetrahidrotiopiran-3-iletoxi, tetrahidrotiopiran-4-iloxi, 2-tetrahidrotiopiran-4-iletoxi, 1-oxotetrahidrotiopiran-3-iloxi, 2-(1-oxotetrahidrotiopiran-3-il)etoxi, 1,1-dioxotetrahidrotiopiran-3-iloxi, 2-(1,1-dioxotetrahidrotiopiran-3-il)etoxi, 1-oxotetrahidrotiopiran-4-iloxi, 2-(1-oxotetrahidrotiopiran-4-il)etoxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, 2-(1,1-dioxotetrahidrotiopiran-4-il)etoxi, 3-tetrahidrotiopiran-3-ilpropoxi, 3-(1,1-dioxotetrahidrotiopiran-3-il)propoxi, 3-(1-oxotetrahidrotiopiran-3-il)propoxi, 3-tetrahidrotiopiran-4-ilpropoxi, 3-(1-oxotetrahidrotiopiran-4-il)propoxi, 3-(1,1-dioxotetrahidrotiopiran-4-il)propoxi, tetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, 2-tetrahidrotien-3-iletoxi, 2-(1, 1-dioxotetrahidrotien-3-il)etoxi, 2-(1-oxotetrahidrotien-3-il)etoxi, 3-tetrahidrotien-3-ilpropoxi, 3-(1,1-dioxotetrahidrotien-3-il)propoxi, 3-(1-oxotetrahidrotien-3-il)propoxi, azetidin-3-iloxi, 2-azetidin-3-iletoxi, 3-azetidin-3-ilpropoxi, 2-imidazol-1-iletoxi, 3-imidazol-1-ilpropoxi, 2-(1,2,3-triazol-1-il)etoxi, 2-(1,2,4-triazol-1-il)etoxi, 3-(1,2,3-triazol-1-il)propoxi, 3-(1,2,4-triazol-1-il)propoxi, pirrolidin-1-ilo, morfolino, piperidino, piperazin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahydro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahydro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, homopiperidin-3 -iloxi, homopiperidin-4-iloxi, homopiperidin-3 -ilmetoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi, 3-homopiperazin-1-ilpropoxi, 2-pirrolidin-1-iletilamino, 3-pirrolidin-1-

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ilpropilamino, pirrolidin-3-ilamino, pirrolidin-2-ilmetilamino, 2-pirrolidin-2-iletilamino, 3-pirrolidin-2-ilpropilamino, 2-morfolinoetilamino, 3-morfolinopropilamino, 2-(1,1-dioxotetrahydro-4H-1,4-tiazin-4-il)etilamino, 3-(1,1-dioxotetrahydro-4H-1,4-tiazin-4-il)propilamino, 2-piperidinoetilamino, 3-piperidinopropilamino, piperidin-3-ilamino, piperidin-4-ilamino, piperidin-3-ilmetilamino, 2-piperidin-3-iletilamino, piperidin-4-ilmetilamino, 2-piperidin-4-iletilamino, homopiperidin-3-ilamino, homopiperidin-4-ilamino, homopiperidin-3-ilmetilamino, 2-homopiperidin-1-iletilamino, 3-homopiperidin-1-ilpropilamino, 2-piperazin-1-iletilamino, 3-piperazin-1-ilpropilamino, 2-homopiperazin-1-iletilamino o 3-homopiperazin-1-ilpropilamino,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en el grupo Q¹-Z- se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, CH=CH y C≡C,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q¹-Z- lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxí, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

y en donde cualquier grupo fenilo o heterociclilo en el grupo Q¹-Z lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxí, amino, carbamoilo, metilo, etilo y metoxi, y un grupo piperidin-3-ilmetilo o piperidin-4-ilmetilo en el grupo Q¹-Z es opcionalmente N-sustituido con 2-metoxietilo, 3-metoxipropilo, 2-aminoetilo, 3-aminopropilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperazin-1-iletilo o 3-piperazin-1-ilpropilo, los últimos 8 de los cuales sustituyentes lleva cada uno opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva

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opcionalmente 1 ó 2 sustituyentes oxo;

(r) el grupo Q¹-Z- se selecciona de ciclopentiloxi, ciclohexiloxi, fenoxi, benciloxi, tetrahydrofuran-3-iloxi, tetrahidropiran-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-3-iloxi, 1-oxotetrahidrotiopiran-3-iloxi, 1,1 -dioxotetrahidrotiopiran-3-iloxi, tetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, tetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, 2-imidazol-1-iletoxi, 2-(1,2,4-triazol-1-il)etoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi, homopiperidin-3-ilmetoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q¹-Z- lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

y en donde cualquier grupo fenilo o heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, metilo, etilo y metoxi,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

(s) el grupo Q¹-Z- se selecciona de ciclopentiloxi, ciclohexiloxi, tetrahydrofuran-3-iloxi, tetrahidropiran-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-3-iloxi, tetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-3-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, 1-

oxotetrahidrotiopiran-3-iloxi, 1-oxotetrahidrotiopiran-4-iloxi,
tetrahidrotien-3-iloxi, 1,1-dioxodotetrahidrotien-3-iloxi, 1-
oxotetrahidrotien-3-iloxi, pirrolidin-3-iloxi, pirrolidin-2-iloxi, piperidin-3-
iloxi, piperidin-4-iloxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi y
azetidin-3-iloxi,

y en donde cualquier grupo azetidínilo, pirrolidinilo, piperidinilo u
homopiperidinilo en el grupo Q¹-Z- es opcionalmente N- sustituido por un
sustituyente seleccionado de (1-4C)alquilo, (2-4C)alquenilo, (2-
4C)alquinilo, (2-4C)alcanoilo, (1-4C)alcoxicarbonilo, carbamoilo, N-(1-
4C)alquilcarbamoilo, N,N-di-(1-4C)alquilcarbamoilo y (1-
4C)alquilsulfonilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-
4C)alquilenos en el grupo N-sustituyente se separan opcionalmente por la
inserción en la cadena de un grupo seleccionado de O, NH y CO,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo N-sustituyente
lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente
seleccionado de hidroxilo, amino, metilamino, di-metilamino, etilamino,
dietilamino, carbamoilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo,
acetilo, metoxicarbonilo y etoxicarbonilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva
opcionalmente 1 ó 2 sustituyentes oxo;

(t) el grupo Q¹-Z- se selecciona de ciclopentiloxi, tetrahydrofuran-3-
iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-4-iloxi, 1,1-
dioxotetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi,
tetrahidrotien-3-iloxi, 1,1-dioxodotetrahidrotien-3-iloxi, 1-
oxotetrahidrotien-3-iloxi, pirrolidin-3-iloxi, pirrolidin-2-iloxi, piperidin-3-
iloxi, piperidin-4-iloxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi y
azetidin-3-iloxi,

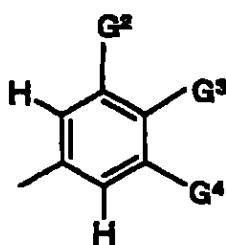
y en donde el grupo azetidínilo, pirrolidinilo, piperidinilo u
homopiperidinilo en el grupo Q¹-Z- es opcionalmente N-sustituido por un
sustituyente seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo,
isobutilo, tert-butilo, alilo, 2-propinilo, acetilo, propionilo,

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metoxycarbonilo, etoxycarbonilo, propoxycarbonilo, tert-butoxycarbonilo, metilsulfonilo, etilsulfonilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-di-metilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-di-metilcarbamoil)etilo, acetilmetilo, 2-acetiletilo, metoxycarbonilmetilo y 2-metoxycarboniletilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

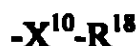
(u) Q² es un grupo arilo de fórmula Ib



Ib

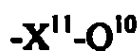
en donde G² y G⁴ cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

G³ se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X¹⁰ es un enlace directo o se selecciona de O y N(R¹⁹), en donde R¹⁹ es hidrógeno o (1-6C)alquilo, y R¹⁸ es halógeno-(1-6C)alquilo, hidroxilo-

(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO, SO₂, N(R²⁰), CO, CH(OR²⁰), CON(R²⁰), N(R²⁰)CO, SO₂N(R²⁰), N(R²⁰)SO₂, C(R²⁰)₂O, C(R²⁰)₂S y N(R²⁰)C(R²⁰)₂, en donde R²⁰ es hidrógeno o (1-6C)alquilo, y Q¹⁰ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde Q¹⁰ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alquenilo, (2-6C)alquinilo, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino,

y en donde cualquier grupo heterociclilo en Q¹⁰ lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,

y a condición que por lo menos uno de G², G³ y G⁴ es distinto de hidrógeno,

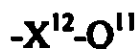
o G³ y G⁴ juntos forman un grupo de fórmula:- -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-, -CH=N-CH=N-, -N=CH-CH=N-, -N=N-CH=CH-, -CH=CH-N=N-, -CH=CH-O-, -O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH₂-CH₂-O-, -O-CH₂-CH₂-, -CH₂-CH₂-S-, -S-CH₂-CH₂-, -O-CH₂-O-, -O-CH₂-CH₂-O-, -S-CH₂-S-, -S-CH₂-CH₂-S-, -CH=CH-NH-, -NH-CH=CH-, -

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CH₂-CH₂-NH-, -NH-CH₂-CH₂-, -N=CH-NH-, -NH-CH=N-, -NH-CH₂-NH-,
 -, -O-CH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH₂-NH-, -NH-CH₂-
 O-, -S-CH₂-NH-, -NH-CH₂-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -
 CH=N-S-, -O-NH-CH₂-, -CH₂-NH-O-, -S-NH-CH₂-, -CH₂-NH-S-, -NH-
 N=CH-, -CH=N-NH-, -NH-NH-CH₂-, -CH₂-NH-NH-, -N=N-NH- o -NH-
 N=N-,

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y el anillo heteroarilo o heterocíclico, bicíclico, de 9 o 10 miembros, formado cuando G³ y G⁴ juntos se enlazan lleva opcionalmente en la porción heteroarilo o heterocíclica del anillo bicíclico 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, (1-6C)alquilo, (2-8C)alqueno, (2-8C)alquino, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, o de un grupo de la fórmula:



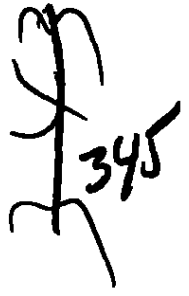
en donde X¹² es un enlace directo o se selecciona de O, SO, SO₂, N(R²¹) y CO, en donde R²¹ es hidrógeno o (1-6C)alquilo y Q¹¹ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi, y cualquier anillo heterocíclico bicíclico así formado lleva opcionalmente 1 ó 2 grupos oxo o tioxo;

(v) Q² es un grupo arilo de fórmula Ib en donde

G² es hidrógeno,

G⁴ se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alqueno, (2-8C)alquino, (1-6C)alcoxi, (2-6C)alquenoilo, (2-6C)alquinoilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

G³ se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alqueno, (2-8C)alquino, (1-6C)alcoxi, (2-6C)alquenoilo, (2-6C)alquinoilo, (1-6C)alquilo, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-



6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^{10} es un enlace directo o se selecciona de O y N(R^{19}), en donde R^{19} es hidrógeno o (1-6C)alquilo, y R^{18} es halógeno-(1-6C)alquilo, hidroxí-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO, SO₂, N(R^{20}), CO, CH(OR²⁰), CON(R^{20}), N(R^{20})CO, SO₂N(R^{20}), N(R^{20})SO₂, C(R^{20})₂O, C(R^{20})₂S y N(R^{20})C(R^{20})₂, en donde R^{20} es hidrógeno o (1-6C)alquilo, y Q^{10} es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

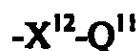
y en donde Q^{10} lleva opcionalmente 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxí, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino,

y en donde cualquier grupo heterociclilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,

y a condición que por lo menos uno de G^3 y G^4 es distinto de hidrógeno,

o G^3 y G^4 juntos forman un grupo de fórmula :- $-CH=CH-CH=CH-$, $-N=CH-CH=CH-$, $-CH=N-CH=CH-$, $-CH=CH-N=CH-$, $-CH=CH-CH=N-$, $-N=CH-N=CH-$, $-CH=N-CH=N-$, $-N=CH-CH=N-$, $-N=N-CH=CH-$, $-CH=CH-N=N-$, $-CH=CH-O-$, $-O-CH=CH-$, $-CH=CH-S-$, $-S-CH=CH-$, $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-CH_2-CH_2-S-$, $-S-CH_2-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-S-CH_2-S-$, $-S-CH_2-CH_2-S-$, $-CH=CH-NH-$, $-NH-CH=CH-$, $-CH_2-CH_2-NH-$, $-NH-CH_2-CH_2-$, $-N=CH-NH-$, $-NH-CH=N-$, $-NH-CH_2-NH-$, $-O-CH=N-$, $-N=CH-O-$, $-S-CH=N-$, $-N=CH-S-$, $-O-CH_2-NH-$, $-NH-CH_2-O-$, $-S-CH_2-NH-$, $-NH-CH_2-S-$, $-O-N=CH-$, $-CH=N-O-$, $-S-N=CH-$, $-CH=N-S-$, $-O-NH-CH_2-$, $-CH_2-NH-O-$, $-S-NH-CH_2-$, $-CH_2-NH-S-$, $-NH-N=CH-$, $-CH=N-NH-$, $-NH-NH-CH_2-$, $-CH_2-NH-NH-$, $-N=N-NH-$ o $-NH-N=N-$,

y el anillo heteroarilo o heterocíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la porción heteroarilo o heterocíclica del anillo bicíclico 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, o de un grupo de la fórmula:



en donde X^{12} es un enlace directo o se selecciona de O, SO, SO₂, N(R²¹) y CO, en donde R²¹ es hidrógeno o (1-6C)alquilo y Q^{11} es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi, y cualquier anillo heterocíclico bicíclico así formado lleva opcionalmente 1 ó 2 grupos oxo o tioxo;

(w) Q^2 es un grupo arilo de fórmula Ib en donde

G^2 es hidrógeno,

G^3 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxí, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino, y a condición que por lo menos uno de G^3 y G^4 es distinto de H;

(x) Q^2 es un grupo arilo de fórmula Ib en donde

G^2 es hidrógeno,

G^3 y G^4 cada independientemente se selecciona de halógeno, trifluorometilo, ciano, hidroxí, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino;

(y) Q^2 es un grupo arilo de fórmula Ib en donde G^2 es H y cada uno de G^3 y G^4 independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, (1-6C)alquilo, (2-8C)alquenilo y (2-8C)alquinilo,

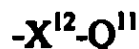
y a condición que por lo menos uno de G^3 y G^4 es distinto de H;

(z) Q^2 es un grupo arilo de fórmula Ib en donde G^2 es H y cada uno de G^3 y G^4 independientemente se selecciona de hidrógeno, hidroxí, fluoro, cloro, bromo, trifluorometilo, metilo, etilo, vinilo, alilo, isopropenilo, etinilo y 1-propinilo,

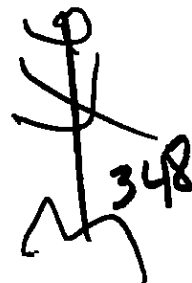
y a condición que por lo menos uno de G^3 y G^4 es distinto de H,

(aa) Q^2 es un grupo arilo de fórmula Ib en donde G^3 y G^4 juntos forman un grupo de fórmula:- $-\text{CH}=\text{CH}-\text{NH}-$, $-\text{NH}-\text{CH}=\text{CH}-$, $-\text{NH}-\text{N}=\text{CH}-$, $-\text{CH}=\text{N}-\text{NH}-$, $-\text{S}-\text{N}=\text{CH}-$ o $-\text{CH}=\text{N}-\text{S}-$,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la porción heteroarilo del anillo bicíclico 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxí, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, o de un grupo de la fórmula:



en donde X^{12} es un enlace directo o se selecciona de O, SO, SO_2 , $\text{N}(\text{R}^{21})$ y CO, en donde R^{21} es hidrógeno o (1-6C)alquilo y Q^{11} es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que

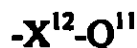


pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi, y cualquier anillo heterocíclico bicíclico así formado lleva opcionalmente 1 ó 2 grupos oxo o tioxo,

y G^2 se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino;

(bb) Q^2 es un grupo arilo de fórmula Ib en donde G^3 y G^4 juntos forman un grupo de fórmula:- $-CH=CH-NH-$, $-NH-CH=CH-$, $-NH-N=CH-$, $-CH=N-NH-$, $-S-N=CH-$ o $-CH=N-S-$,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo seleccionado de trifluorometilo, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo, (1-4C)alcoxycarbonilo, carbamoilo, N-(1-4C)alquilcarbamoilo, N,N-di-(1-4C)alquilcarbamoilo y (1-4C)alquilsulfonilo, o de un grupo de la fórmula:



en donde X^{12} es un enlace directo o se selecciona de SO_2 y CO, en donde R^{21} es hidrógeno o (1-6C)alquilo y Q^{11} es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, el cual lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de ciano, halógeno, hidroxilo, (1-6C)alquilo y (1-6C)alcoxi,

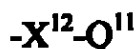
y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en un átomo de carbono disponible en la porción heteroarilo del anillo bicíclico 1 sustituyente seleccionado de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, (1-6C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, y cualquier anillo heterocíclico bicíclico así formado lleva opcionalmente 1 ó 2 grupos oxo o tioxo,

y G^2 se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino;

(cc) Q^2 es un grupo arilo de fórmula Ib en donde G^3 y G^4 juntos forman

un grupo de fórmula:- -CH=CH-NH- , -NH-CH=CH- , -NH-N=CH- o -CH=N-NH- ,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo de la fórmula:



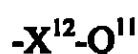
en donde X^{12} es un enlace directo o se selecciona de SO_2 y CO , en donde Q^{11} es fenilo, bencilo, 2-feniletilo, 2-furilo, furfurilo, 3-furilo, 3-furilmetilo, 2-oxazolilo, 4-oxazolilo, 2-oxazolilmetilo, 4-oxazolilmetilo, 2-imidazolilo, 4-imidazolilo, 2-imidazolilmetilo, 4-imidazolilmetilo, 2-, 3- ó 4-piridilo, 2-, 3- ó 4-piridilmetilo, 2-(2-, 3- ó 4-piridil)etilo, 2-, 4- ó 5- pirimidinilo, 2-, 4- ó 5- pirimidinilmetilo, 2-(2-, 4- ó 5- pirimidinil)etilo, 1,2,4-triazol-3-ilo, 1,2,4-triazol-5-ilmetilo, 1,2,4-triazol-3-ilmetilo, 1,2,4-triazol-5-il 2-tienilo, 3-tienilo, 2-tienilmetilo, 3-tienilmetilo, 2-(2-tienil)etilo, 2-(3-tienil)etilo, 2-tiazolilo, 4-tiazolilo, 2-tiazolilmetilo, 4-tiazolilmetilo, 1,2,5-tiadiazol-3-ilo, 1,2,5-tiadiazol-3-ilmetilo, 2-(1,2,5-tiadiazol-3-il)etilo el cual lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, hidroxilo, metilo y etilo,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en un átomo de carbono disponible en la porción heteroarilo del anillo bicíclico 1 sustituyente seleccionado de fluoro, cloro, bromo, ciano, hidroxilo, amino, metilo, etilo, vinilo, etinilo, metilamino y di-metilamino,

y G^2 se selecciona de hidrógeno, fluoro, cloro, bromo, trifluorometilo, ciano, hidroxilo, amino, metilo, etilo, vinilo, etinilo, metilamino y di-metilamino;

(dd) Q^2 es un grupo arilo de fórmula Ib en donde G^3 y G^4 juntos forman un grupo de fórmula:- -NH-CH=CH- o -NH-N=CH- ,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo de la fórmula:



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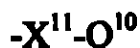


en donde X^{12} es un enlace directo o es SO_2 y Q^{11} es bencilo o 2-piridilmetilo, el cual lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, hidroxilo y metilo,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la posición 3 en la porción heteroarilo del anillo bicíclico 1 sustituyente seleccionado de fluoro, cloro, bromo, ciano, hidroxilo, amino, metilo, etilo y etinilo,

y G^2 se selecciona de hidrógeno, fluoro, cloro, bromo, ciano, hidroxilo, amino, metilo, etilo y etinilo;

(ee) Q^2 es un grupo arilo de fórmula Ib en donde G^3 se selecciona de carbamoilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, o de un grupo de la fórmula:



en donde X^{11} es $CON(R^{20})$, en donde R^{20} es hidrógeno o (1-6C)alquilo, y Q^{10} es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde Q^{10} lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, y en donde cualquier grupo heterociclilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,

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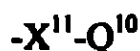
y G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxí, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino; (ff) Q^2 es un grupo arilo de fórmula Ib en donde G^3 se selecciona de un grupo de la fórmula:



en donde X^{11} es CO y Q^{10} es un nitrógeno de 5 a 10 miembros que contiene un grupo heterocíclico enlazado a X^{11} por un átomo de nitrógeno,

y Q^{10} lleva opcionalmente 1 ó 2 sustituyentes seleccionados de halógeno, ciano, hidroxí, amino, (1-6C)alquilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

y G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxí, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino; (gg) Q^2 es un grupo arilo de fórmula Ib en donde G^3 se selecciona de un grupo de la fórmula:

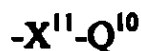


en donde X^{11} es CO y Q^{10} se selecciona de, pirrolidin-1-ilo, piperidino, homopiperidino, morfolino, piperazin-1-ilo, homopiperazin-1-ilo, decahidroquinolin-1-ilo, y decahidroisoquinolin-2-ilo,

y en donde Q^{10} lleva opcionalmente 1 ó 2 sustituyentes seleccionado de fluoro, cloro, bromo, ciano, hidroxí, metilo y etilo,

y G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, ciano, hidroxí, metilo, etilo y etinilo;

(hh) Q^2 es un grupo arilo de fórmula Ib en donde G^3 se selecciona de un grupo de la fórmula:



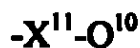
en donde X^{11} es un enlace directo o se selecciona de O, S, SO, SO₂, N(R²⁰), CO, CH(OR²⁰), N(R²⁰)CO, SO₂N(R²⁰), N(R²⁰)SO₂, C(R²⁰)₂O, C(R²⁰)₂S y N(R²⁰)C(R²⁰)₂, en donde R²⁰ es hidrógeno o (1-6C)alquilo, y Q^{10} es arilo, aril-(1-6C)alquilo, heteroarilo y heteroaril-(1-6C)alquilo,

y en donde Q^{10} lleva opcionalmente 1, 2 ó 3 sustituyentes, que



pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, nitro, ciano, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

y G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino;
(ii) Q^2 es un grupo arilo de fórmula Ib en donde G^3 se selecciona de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO_2 , $N(R^{20})$, CO, $CH(OR^{20})$, $C(R^{20})_2O$, $C(R^{20})_2NR^{20}$, y $C(R^{20})_2S$, en donde R^{20} es hidrógeno, metilo o etilo, y Q^{10} es un grupo fenilo, bencilo, 2-feniletilo, naftilo, naftilmetilo o 2-naftiletilo el cual se sustituye opcionalmente con 1 ó 2 sustituyentes seleccionados de fluoro, cloro, bromo, trifluorometilo, nitro, metilo, etilo, isopropilo, vinilo, etinilo y ciano,

o Q^{10} es una fracción heteroarilo seleccionada de furilo, furilmetilo, 2-(furi)etilo, tienilo, tienilmetilo, 2-(tienil)etilo, oxazolilo, oxazolilmetilo, 2-(oxazolil)etilo, isoxazolilo, isoxazolilmetilo, 2-(isoxazolil)etilo, imidazolilo, imidazolilmetilo, 2-(imidazolil)etilo, tiazolilo, tiazolilmetilo, 2-(tiazolil)etilo, 1,2,4-triazolilo, 1,2,4-triazolilmetilo, 2-(1,2,4-triazolil)etilo, 1,2,5-tiadiazolilo, 1,2,5-tiadiazolilmetilo, 2-(1,2,5-tiadiazolil)etilo, piridilo, piridilmetilo, 2-(piridil)etilo, pirimidinilo, pirimidinilmetilo, 2-(pirimidinil)etilo, 1,3-benzodioxolilo, 1,3-benzodioxolilmetilo, 2-(1,3-benzodioxolil)etilo, quinolinilo, quinolinilmetilo, 2-(quinolinil)etilo, isoquinolinilo, isoquinolinilmetilo, 2-(isoquinolinil)etilo, quinazolinilo, quinazolinilmetilo y 2-(quinazolinil)etilo, el cual se sustituye opcionalmente con uno o dos sustituyentes seleccionado de fluoro, cloro, bromo, nitro, metilo, trifluorometilo, etilo, isopropilo, metoxi y etoxi;

y cada uno de G^2 y G^4 independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, trifluorometilo, metilo, etilo, vinilo, alilo, etinilo, metilamino y di-metilamino;

(jj) Q^2 es un grupo arilo de fórmula Ib en donde G^3 se selecciona de un grupo de la fórmula:

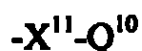


en donde X^{11} es un enlace directo o se selecciona de O, S, SO_2 , $N(R^{20})$, CO, $CH(OR^{20})$, $C(R^{20})_2O$, $C(R^{20})_2NR^{20}$, y $C(R^{20})_2S$, en donde R^{20} es hidrógeno o metilo, y Q^{10} es un grupo fenilo o bencilo el cual se sustituye opcionalmente con 1 ó 2 sustituyentes seleccionado de fluoro, cloro, bromo, nitro, trifluorometilo, metilo, etinilo y ciano,

o Q^{10} es una fracción heteroarilo seleccionada de 2-furilo, furfurilo, 3-furilmetilo, 2- ó 3-tienilo, 2- ó 3-tienilmetilo, 2-,4- ó 5-oxazolilo, 2-,4- ó 5-oxazolilmetilo, 3-,4- ó 5-isoxazolilo, 3-,4- ó 5-isoxazolilmetilo, 2-,4- ó 5-1H-imidazolilo, 2-,4- ó 5-1H-imidazolilmetilo, 2-,4- ó 5-tiazolilo, 2-,4- ó 5-tiazolilmetilo, 3- ó 5-(1H-1,2,4-triazolil), 3- ó 5-(1H-1,2,4-triazolil)metilo, 3- ó 4-(1,2,5-tiadiazolil), 3- ó 4-(1,2,5-tiadiazolil)metilo, 2- 3- ó 4-piridilo, 2-, 3- ó 4-piridilmetilo, 2-, 4- ó 5-pirimidinilo, 2-, 4- ó 5-pirimidinilmetilo, 1,3-benzodioxol-4-ilo, 1,3-benzodioxol-5-ilo, 1,3-benzodioxol-4-ilmetilo, 2-(1,3-benzodioxol-4-il)etilo, 2-(1,3-benzodioxol-5-il)etilo, 1,3-benzodioxolilmetilo, 2-, 3-, 4-, 5-, 6-, 7- ó 8-quinolinilo, 2-, 3-, 4-, 5-, 6-, 7- ó 8-quinolinilmetilo, 1-, 3-, 4-, 5-, 6-, 7- ó 8-isoquinolinilo, 1-, 3-, 4-, 5-, 6-, 7- ó 8-isoquinolinilmetilo, 2-, 3-, 4-, 5-, 6-, 7- ó 8-quinazolinilo y 2-, 3-, 4-, 5-, 6-, 7- ó 8-quinazolinilmetilo, el cual se sustituye opcionalmente con uno o dos sustituyentes seleccionados de fluoro, cloro, bromo, metilo, etilo, trifluorometilo, etinilo, y ciano;

y cada uno de G^2 y G^4 independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, trifluorometilo, metilo, etilo, vinilo, alilo, etinilo y ciano;

(kk) Q^2 es un grupo arilo de fórmula Ib en donde G^3 se selecciona de un grupo de la fórmula:

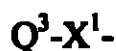


en donde X^{11} es un enlace directo o se selecciona de O, S, $N(R^{20})$, CO, $CH(OR^{20})$ y $C(R^{20})_2NR^{20}$, en donde R^{20} es hidrógeno o metilo, y Q^{10} es un grupo fenilo o bencilo el cual se sustituye opcionalmente con 1 ó 2

sustituyentes seleccionados de fluoro, cloro, bromo, nitro, metilo, etilo, isopropilo, etinilo y ciano,

o Q^{10} es una fracción heteroarilo seleccionado de 2-1H-imidazolilo, 2-1H-imidazolilmetilo, 4-tiazolilmetilo, 2-tienilmetilo, 3-(1,2,5-tiadiazolil), 3-(1,2,5-tiadiazolil)metilo, 3-isoxazolilmetilo, 2- ó 3-piridilo, 2- ó 3-piridilmetilo, 8-quinolinilo, y 8-quinolinilmetilo, la cual fracción se sustituye opcionalmente con uno o dos sustituyentes seleccionados de fluoro, cloro, bromo, trifluorometilo, metilo, etinilo y ciano; y cada uno de G^2 y G^4 independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, metilo, y etinilo;

(II) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de halógeno, trifluorometilo, ciano, isociano, nitro, hidroxilo, mercapto, amino, formilo, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alquenilo, (2-6C)alquinilo, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^1 es un enlace directo o se selecciona de O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ y N(R⁴)C(R⁴)₂, en donde cada R⁴ es, independientemente, hidrógeno o (1-6C)alquilo, y Q^3 es (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en un sustituyente R^1 se separan opcionalmente por la

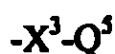
inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH y C≡C en donde R⁵ es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo CH₂=CH- ó HC≡C- en un sustituyente R¹ lleva opcionalmente en la posición terminal CH₂= ó HC≡ un sustituyente seleccionado de halógeno, carboxi, carbamoilo, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquilo o de un grupo de la fórmula:



en donde X² es un enlace directo o se selecciona de CO y N(R⁶)CO, en donde R⁶ es hidrógeno o (1-6C)alquilo, y Q⁴ es heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R¹ lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxí, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X³ es un enlace directo o se selecciona de O, S, SO, SO₂, N(R⁷), CO, CH(OR⁷), CON(R⁷), N(R⁷)CO, SO₂N(R⁷), N(R⁷)SO₂, C(R⁷)₂O, C(R⁷)₂S y N(R⁷)C(R⁷)₂, en donde R⁷ es hidrógeno o (1-6C)alquilo, y Q³ (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes,

seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alquenilo, (2-6C)alquinilo, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, amino(2-6C)alcanoilo, N-(1-6C)alquilamino(2-6C)alcanoilo, N,N-di-[(1-6C)alquil]amino(2-6C)alcanoilo, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, y N-(1-6C)alquil-(1-6C) alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^4 es un enlace directo o se selecciona de O y N(R^9), en donde R^9 es hidrógeno o (1-6C)alquilo, y R^8 es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, carboxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo, (1-6C)alcoxycarbonilamino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo, (2-6C)alcanoilo-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo, o de un grupo de la fórmula:

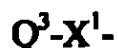


en donde X^5 es un enlace directo o se selecciona de O, CO y N(R^{10}), en donde R^{10} es hidrógeno o (1-6C)alquilo, y Q^6 es heterociclilo o heterocicli-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

(mm) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-



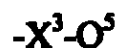
6C)alqueniloxy y (2-6C)alquiniloxy, o de un grupo de la fórmula:



en donde X^1 es un enlace directo o es O, y Q^3 es heterociclilo o heterociclíl-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, $N(R^5)$, CO, $CH=CH$ y $C\equiv C$ en donde R^5 es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, amino, (1-6C)alcoxi, (1-6C)alquilsulfonilo, (1-6C)alquilamino y di-[(1-6C)alquil] amino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O y $N(R^7)$, en donde R^7 es hidrógeno o (1-6C)alquilo, y Q^5 es heterociclilo o heterociclíl-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, ciano, hidroxilo, amino, carboxilo, carbamoilo, formilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, $\underline{N}$ -(1-6C)alquilcarbamoilo, $\underline{N,N}$ -di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxy, o de un grupo de la fórmula:



en donde X^4 es un enlace directo o se selecciona de O y $N(R^9)$, en donde R^9 es hidrógeno o (1-6C)alquilo, y R^8 es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, $\underline{N}$ -(1-6C)alquilcarbamoilo-(1-6C)alquilo, $\underline{N,N}$ -di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo, o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la

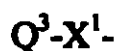
fórmula:



en donde X^5 es un enlace directo y Q^6 es heterociclilo o heterocicliil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

(nn) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-6C)alcoxi, (1-6C)alquenilo, (1-6C)alkinilo, o de un grupo de la fórmula:



en donde X^1 es un enlace directo o es O y Q^3 es tetrahydrofuran-3-ilo, tetrahydrofurfurilo, 2-(tetrahydrofuran-2-il)etilo, tetrahydrofuran-3-ilmetilo, 2-(tetrahydrofuran-3-il)etilo, 1-, 2- ó 3-pirrolidinilo, morfolino, tiamorfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, 1-, 3- ó 4-homopiperidinilo, piperazin-1-ilo, homopiperazin-1-ilo, 1-, 2- ó 3-pirrolidinilmetilo, morfolinometilo, tiamorfolinometilo, piperidinometilo, 2-, 3- ó 4-piperidinilmetilo, 1-, 3- ó 4-homopiperidinilmetilo, piperazin-1-ilmetilo, homopiperazin-1-ilmetilo, 2-pirrolidin-1-iletilo, 2-pirrolidin-2-iletilo, 2-pirrolidin-3-iletilo, 3-pirrolidin-1-ilpropilo, 3-pirrolidin-2-ilpropilo, 3-pirrolidin-3-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-tiamorfolinoetilo, 3-tiamorfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperidin-2-iletilo, 2-piperidin-3-iletilo, 2-piperidin-4-iletilo, 3-piperidin-2-ilpropilo, 3-piperidin-3-ilpropilo, 3-piperidin-4-ilpropilo, 2-homopiperidin-1-iletilo, 3-homopiperidin-1-ilpropilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo, 2-homopiperazin-1-iletilo ó 3-homopiperazin-1-ilpropilo, y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(CH₃), CH=CH y C≡C,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R^1 lleva

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opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxilo, amino, metoxi, etoxi, metilsulfonilo, metilamino y dimetilamino, o de un grupo de la fórmula:



en donde X³ es un enlace directo o se selecciona de O, NH y N(CH₃) y Q⁵ es tetrahydrofuran-2-ilo, tetrahydrofuran-3-ilo, tetrahydrofurfurilo, 2-(tetrahydrofuran-2-il)etilo, tetrahydrofuran-3-ilmetilo, 2-(tetrahydrofuran-3-il)etilo, pirrolidin-1-ilo, pirrolidin-2-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, 2-piperazin-1-iletilo o 3-piperazin-1-ilpropilo,

y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, formilo, amino, carbamoilo, (1-4C)alquilo, (1-4C)alcoxi, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alquilamino, di-[(1-4C)alquil]amino, (2-4C)alcanoilo, (1-4C)alquilsulfonilo, (1-4C)alcoxicarbonilo, N-(1-4C)alquilcarbamoilo y N,N-di-[(1-4C)alquil]carbamoilo, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X⁴ es un enlace directo o se selecciona de O y NH, y R⁸ es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, fluorometilo, 2-fluoroetilo, clorometilo, 2-cloroetilo, aminometilo, 2-aminoetilo, 3-aminopropilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-etilaminoetilo, 3-etilaminopropilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, acetilmetilo, acetamidometilo, carbamoilmetilo, 2-carbamoiletilo, N-metilcarbamoilmetilo, N,N-di-metilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-di-metilcarbamoil)etilo, cianometilo,

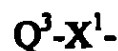
cianoetilo, metoxycarbonilaminometilo, etoxycarbonilaminometilo o tert-butoxycarbonilaminometilo, o de un grupo de la fórmula:



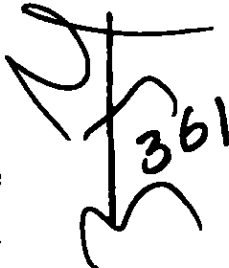
en donde X^5 es un enlace directo o se selecciona de O y NH, y Q^6 es pirrolidin-2-ilo, pirrolidin-3-ilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, tetrahydrofuran-2-ilo, tetrahydrofuran-3-ilo, tetrahydrofurfurilo, 2-(tetrahydrofuran-2-il)etilo, tetrahydrofuran-3-ilmetilo, 2-(tetrahydrofuran-3-il)etilo, piperidin-4-ilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo o 3-piperazin-1-ilpropilo, cada uno de los cuales lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, hidroxilo, metilo, etilo, metoxi, etoxi, amino, metilamino y di-metilamino,

y en donde cualquier grupo heterociclilo en un sustituyente R^1 lleva opcionalmente 1 sustituyente oxo;

(oo) m es 1 y el grupo R^1 se localiza en la posición 7 y es un grupo de la fórmula:



en donde X^1 es un enlace directo o es O y Q^3 es 1-, 2- ó 3-pirrolidinilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, 1-, 3- ó 4-homopiperidinilo, piperazin-1-ilo, homopiperazin-1-ilo, pirrolidin-1-ilmetilo, pirrolidin-2-ilmetilo, pirrolidin-3-ilmetilo, 2-pirrolidin-1-iletilo, 2-pirrolidin-2-iletilo, 2-pirrolidin-3-iletilo, 3-pirrolidin-1-ilpropilo, 3-pirrolidin-2-ilpropilo, 3-pirrolidin-3-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, piperidin-2-ilmetilo, piperidin-3-ilmetilo, piperidin-4-ilmetilo, 2-piperidin-2-iletilo, 2-piperidin-3-iletilo, 2-piperidin-4-iletilo, 3-piperidin-2-ilpropilo, 3-piperidin-3-ilpropilo, 3-piperidin-4-ilpropilo, 2-homopiperidin-1-iletilo, 3-homopiperidin-1-ilpropilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo, 2-homopiperazin-1-iletilo ó 3-homopiperazin-1-ilpropilo,



y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, formilo, amino, carbamoilo, (1-4C)alquilo, (1-4C)alcoxi, (2-4C)alquenilo, (2-4C)alquinilo, (1-4C)alquilamino, di-[(1-4C)alquil]amino, (2-4C)alcanoilo, (1-4C)alquilsulfonilo, (1-4C)alcoxycarbonilo, N-(1-4C)alquilcarbamoilo y N,N-di-[(1-4C)alquil]carbamoilo, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X^4 es un enlace directo o se selecciona de O y NH, y R^8 es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, fluorometilo, 2-fluoroetilo, clorometilo, 2-cloroetilo, aminometilo, 2-aminoetilo, 3-aminopropilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-etilaminoetilo, 3-etilaminopropilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, acetilmetilo, acetamidometilo, carbamoilmetilo, 2-carbamoiletilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-(N,N-dimetilcarbamoil)etilo, cianometilo, cianoetilo, metoxycarbonilaminometilo o etoxycarbonilaminometilo, y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1 sustituyente oxo;

(pp) m es 1 y el grupo R^1 se localiza en la posición 7 y es un grupo de la fórmula:



en donde X^1 es O y Q^3 se selecciona de heterociclil-propilo o heterociclil-butilo, en donde dicho grupo heterociclilo contiene por lo menos 1 átomo de nitrógeno,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, $N(R^5)$, CO, $CH=CH$ y $C\equiv C$ en donde R^5 es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de



halógeno, hidroxilo, carbamoilo, (1-4C)alquilo, (1-4C)alcoxi, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo, (1-4C)alquilsulfonilo, (1-4C)alcoxycarbonilo, N-(1-4C)alquilcarbamoilo y N,N-di-[(1-4C)alquil]carbamoilo, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X^4 es un enlace directo o se selecciona de O y NH, y R^8 es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, fluorometilo, 2-fluoroetilo, clorometilo, 2-cloroetilo, acetilmetilo, acetamidometilo, carbamoilmetilo, 2-carbamoiletilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-N-metilcarbamoiletilo, 2-(N,N-dimetilcarbamoil)etilo, cianometilo, cianoetilo, metoxycarbonilaminometilo o etoxycarbonilaminometilo,

y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1 sustituyente oxo;

(qq) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de 3-pirrolidin-1-ilpropoxi, 3-pirrolidin-2-ilpropoxi, 3-pirrolidin-3-ilpropoxi, 3-piperidinopropoxi, 3-piperidin-2 ilpropoxi, 3-piperidin-3-ilpropoxi, piperidin-4-ilpropoxi, 3-morfolinopropoxi, 3-morfolin-2-ilpropoxi, 3-morfolin-3-ilpropoxi, 3-piperazin-1-ilpropoxi y 3-piperazin-2-ilpropoxi,

y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de hidroxilo, carbamoilo, (1-4C)alquilo, (1-4C)alcoxi, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo, (1-4C)alquilsulfonilo, (1-4C)alcoxycarbonilo, N-(1-4C)alquilcarbamoilo y N,N-di-[(1-4C)alquil]carbamoilo, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X^4 es un enlace directo o se selecciona de O y NH, y R^8 es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, fluorometilo, 2-fluoroetilo, clorometilo, 2-cloroetilo, acetilmetilo, acetamidometilo, carbamoilmetilo, 2-carbamoiletilo, N-

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metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-dimetilcarbamoil)etilo, cianometilo, cianoetilo, metoxycarbonilaminometilo o etoxycarbonilaminometilo, y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente 1 sustituyente oxo;

(rr) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de 3-pirrolidin-1-ilpropoxi, 3-piperidinopropoxi, 3-morfolinopropoxi y 3-piperazin-1-ilpropoxi y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente un sustituyente hidroxil y en donde cualquier grupo piperazinilo en R¹ lleva opcionalmente un sustituyente seleccionado de hidroxil, metilo, etilo, isopropilo, acetilo, alilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-di-metilcarbamoilmetilo, acetilmetilo y cianometilo,

y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente un sustituyente oxo;

(ss) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de 4-pirrolidin-1-ilbutoxi, 4-pirrolidin-2-ilbutoxi, 4-pirrolidin-3-ilbutoxi, 4-piperidinobutoxi, 4-piperidin-2-ilbutoxi, 4-piperidin-3-ilbutoxi, 4-piperidin-4-ilbutoxi, 4-morfolinobutoxi, 4-morfolin-2-ilbutoxi, 4-morfolin-3-ilbutoxi, 4-piperazin-1-ilbutoxi y 4-piperazin-2-ilbutoxi, y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de hidroxil, carbamoilo, (1-4C)alquilo, (1-4C)alcoxi, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo, (1-4C)alquilsulfonilo, (1-4C)alcoxicarbonilo, N-(1-4C)alquilcarbamoilo y N,N-di-[(1-4C)alquil]carbamoilo, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



en donde X⁴ es un enlace directo o se selecciona de O y NH, y R⁸ es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, fluorometilo, 2-fluoroetilo, clorometilo, 2-cloroetilo, acetilmetilo, acetamidometilo, carbamoilmetilo, 2-carbamoiletilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-(N,N-dimetilcarbamoil)etilo,

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cianometilo, cianoetilo, metoxycarbonilaminometilo
etoxycarbonilaminometilo,

y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente 1
sustituyente oxo;

(tt) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de 4-
pirrolidin-1-ilbutoxi, 4-piperidinobutoxi, 4-morfolinobutoxi y 4-piperazin-
1-ilbutoxi, y en donde cualquier grupo heterociclilo en R¹ lleva
opcionalmente un sustituyente hidroxilo y en donde cualquier grupo
piperazinilo en R¹ lleva opcionalmente un sustituyente seleccionado de
hidroxilo, metilo, etilo, isopropilo, acetilo, alilo, 2-metoxietilo,
carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo y
cianometilo,

y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente
un sustituyente oxo;

(uu) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de 2-
pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-
piperidinopropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-
morfolinoetoxi, 3-morfolinopropoxi, 2-piperazin-1-iletoxi y 3-piperazin-1-
ilpropoxi,

y en donde cualquier grupo piperazinilo en R¹ lleva opcionalmente
un sustituyente seleccionado de hidroxilo, metilo, etilo, isopropilo, acetilo,
alilo, 2-propinilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo,
N,N-dimetilcarbamoilmetilo y cianometilo,

y en donde cualquier grupo heterociclilo en R¹ lleva opcionalmente
un sustituyente oxo;

(vv) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de 2-
pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-
piperidinopropoxi, 2-piperazin-1-ilethioxi y 3-piperazin-1-ilpropoxi,

y en donde cualquier grupo piperazinilo en R¹ lleva opcionalmente
un sustituyente seleccionado de hidroxilo, metilo, acetilo, alilo, 2-
metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo y N,N-
dimetilcarbamoilmetilo,

y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente un sustituyente oxo;

(ww) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de 3-pirrolidin-1-ilpropoxi y 3-morfolinopropoxi,

y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente un sustituyente oxo;

(xx) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de metoxi, 2-metoxietoxi, 3-pirrolidin-1-ilpropoxi, 3-morfolinopropoxi y 3-piperazin-1-ilpropoxi,

y en donde cualquier grupo piperazinilo en R^1 lleva opcionalmente un sustituyente seleccionado de carbamoilmetilo, N-metilcarbamoilmetilo y N,N-dimetilcarbamoilmetilo,

(yy) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-6C)alcoxi, (2-6C)alqueniloxi y (2-6C)alquiniloxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH y $N(CH_3)$,

y en donde cualquier grupo CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxi, etoxi, metilsulfonilo, metilamino y dimetilamino;

(zz) m es 1 y el grupo R^1 se localiza en la posición 7 y es (1-3C)alcoxi o (1-3C)alcoxi(1-3C)alcoxi, por ejemplo metoxi, etoxi y 2-metoxi;

(aaa) m es 1 y el grupo R^1 se localiza en la posición 7 y es metoxi;

(bbb) Q^1 es (3-7C)cicloalquilo, (3-7C)cicloalquenilo o heterociclilo,

y en donde cualquier grupo CH_2 ó CH_3 en el grupo Q^1 -Z- lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfonilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-

6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, amino(2-6C)alcanoilo, N-(1-6C)alquilamino(2-6C)alcanoilo, N,N-di-[(1-6C)alquil]amino(2-6C)alcanoilo, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X⁸ es un enlace directo o se selecciona de O y N(R¹⁶), en donde R¹⁶ es hidrógeno o (1-6C)alquilo, y R¹⁵ es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo, (2-6C)alcanoilo-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

(ccc) Q¹ se selecciona de (3-7C)cicloalquilo y un anillo heterociclilo de 4, 5, 6 ó 7 miembros enlazados a Z por un átomo de carbono,

y en donde cualquier grupo NH en un grupo heterociclilo en Q¹ lleva opcionalmente un sustituyente seleccionado de formilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo,

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aminoalcanoilo, (1-4C)alcoxycarbonilo, carbamoilo, sulfamoilo, N-(1-4C)alquilcarbamoilo, N,N-di-(1-4C)alquilcarbamoilo, N-(1-4C)alquilsulfamoilo, N,N-di-(1-4C)alquilsulfamoilo y (1-4C)alquilsulfonilo, o de un grupo de la fórmula:



en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-4C)alquilo, hidroxí-(1-4C)alquilo, (1-4C)alcoxi-(1-4C)alquilo, ciano-(1-4C)alquilo, carboxi-(1-6C)alquilo, amino-(1-4C)alquilo, (1-4C)alquilamino-(1-4C)alquilo, di-[(1-4C)alquil]amino-(1-4C)alquilo, carbamoil-(1-4C)alquilo, N-(1-4C)alquilcarbamoil-(1-4C)alquilo, N,N-di-[(1-4C)alquil]carbamoil-(1-4C)alquilo, (2-4C)alcanoil-(1-4C)alquilo o (1-4C)alcoxycarbonil-(1-4C)alquilo,

y en donde cualquier grupo CH ó CH₂ en un grupo (3-7C)cicloalquilo o heterociclilo en el grupo Q¹ lleva opcionalmente 1 sustituyente en cada uno de dicho grupo CH o los 2 sustituyentes en cada uno de dicho grupo CH₂, que pueden ser los mismos o diferentes, seleccionados de halógeno y (1-6C)alquilo, o un sustituyente seleccionado de hidroxí, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo,

(ddd) Z es O y Q¹ se selecciona de un anillo heterociclilo de 4, 5 ó 6 miembros que contiene por lo menos 1 átomo de nitrógeno, enlazándose dicho anillo a Z por un átomo de carbono,

y en donde cualquier grupo NH en un grupo heterociclilo lleva opcionalmente un sustituyente seleccionado de formilo, ciano, (1-

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4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo, (1-4C)alcoxicarbonilo, carbamoilo, N-(1-4C)alquilcarbamoilo, N,N-di-(1-4C)alquilcarbamoilo, N-(1-4C)alquilsulfamoilo, N,N-di-(1-4C)alquilsulfamoilo y (1-4C)alquilsulfonilo, o de un grupo de la fórmula:



en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-4C)alquilo, hidroxí-(1-4C)alquilo, (1-4C)alcoxi-(1-4C)alquilo, ciano-(1-4C)alquilo, carboxi-(1-6C)alquilo, amino-(1-4C)alquilo, (1-4C)alquilamino-(1-4C)alquilo, di-[(1-4C)alquil]amino-(1-4C)alquilo, carbamoil-(1-4C)alquilo, N-(1-4C)alquilcarbamoil-(1-4C)alquilo, N,N-di-[(1-4C)alquil]carbamoil-(1-4C)alquilo, (2-4C)alcanoil-(1-4C)alquilo o (1-4C)alcoxicarbonil-(1-4C)alquilo,

y en donde cualquier grupo heterociclilo en el grupo Q^1 -Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

(eee) Z es O y Q^1 se selecciona de azetidin-3-ilo, pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo, (convenientemente pirrolidin-3-ilo, piperidin-3-ilo o piperidin-4-ilo), y en donde cualquier grupo NH en un grupo heterociclilo en Q^1 lleva opcionalmente un sustituyente seleccionado de formilo, ciano, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo, (1-4C)alcoxicarbonilo, carbamoilo, sulfamoilo, N-(1-4C)alquilcarbamoilo, N,N-di-(1-4C)alquilcarbamoilo, N-(1-4C)alquilsulfamoilo, N,N-di-(1-4C)alquilsulfamoilo y (1-4C)alquilsulfonilo, o de un grupo de la fórmula:



en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-4C)alquilo, hidroxí-(1-4C)alquilo, (1-4C)alcoxi-(1-4C)alquilo, ciano-(1-4C)alquilo, carboxi-(1-4C)alquilo, amino-(1-4C)alquilo, (1-4C)alquilamino-(1-4C)alquilo, di-[(1-4C)alquil]amino-(1-4C)alquilo, carbamoil-(1-4C)alquilo, N-(1-4C)alquilcarbamoil-(1-4C)alquilo, N,N-di-[(1-4C)alquil]carbamoil-(1-4C)alquilo, (2-4C)alcanoil-(1-4C)alquilo o (1-4C)alcoxicarbonil-(1-4C)alquilo,

y en donde cualquier grupo heterociclilo en el grupo Q^1 -Z- lleva

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opcionalmente 1 ó 2 sustituyentes oxo;

(fff) Z es O y Q¹ se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo, y en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q¹ lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo y de un grupo de la fórmula:



en donde X⁸ es un enlace directo, y R¹⁵ es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-di-metilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo, y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q¹-Z- lleva opcionalmente 1 sustituyente oxo;

(ggg) Z es O y Q¹ se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo, y en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q¹ lleva opcionalmente un sustituyente seleccionado de metilo, etilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, 2-fluoroetilo, metoxietil carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, acetilmetilo y metoxycarbonilmetilo,

y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q¹-Z- lleva opcionalmente 1 sustituyente oxo;

(hhh) Z es O y Q¹ se selecciona de un anillo heterociclilo de 5 ó 6 miembros que contiene por lo menos 1 heteroátomo seleccionado de O y S y no heteroátomos de nitrógeno, y en donde dicho anillo heterociclilo se enlaza a Z por un átomo de carbono,

y en donde dicho anillo heterociclilo de 5 ó 6 miembros lleva opcionalmente 1, 2 ó 3 sustituyentes seleccionados de halógeno, (1-6C)alquilo, hidroxí, amino, carboxi, (1-6C)alcoxi y (1-6C)alquiltio,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

(iii) Z es O y Q¹ se selecciona de tetrahidrofuran-3-ilo, tetrahidropiran-3-

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il y tetrahidropiran-4-ilo,

y en donde cualquier grupo tetrahydrofuranilo o tetrahidropiranilo en Q¹ lleva opcionalmente 1 ó 2 sustituyentes seleccionados de fluoro, cloro, hidroxilo, metilo, etilo y amino, y en donde cualquier grupo tetrahydrofuranilo o tetrahidropiranilo en el grupo Q¹-Z- lleva opcionalmente 1 sustituyente oxo;

(iii) Z es O y Q¹ se selecciona de tetrahydrofuran-3-ilo, tetrahidropiran-3-ilo y tetrahidropiran-4-ilo,

y en donde Q¹ lleva opcionalmente un sustituyente oxo;

(kkk) Z es O y Q¹ se selecciona de tetrahydrofuran-3-ilo y piperidin-4-ilo, y en donde cualquier grupo piperidin-4-ilo lleva opcionalmente un sustituyente en la posición 1 seleccionado de metilo, carbamoilmetilo, y N,N-dimetilcarbamoilmetilo;

(III) Q¹ es (3-7C)cicloalquilo, el cual lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, N-(1-6C)alquil-(1-6C)alcanosulfonilamino, y de un grupo de la fórmula:



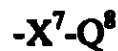
en donde X⁵ es un enlace directo o se selecciona de O, CO y N(R¹⁴), en donde R¹⁴ es hidrógeno o (1-6C)alquilo, y Q⁸ es heterociclilo que contiene nitrógeno o heterociclil-(1-6C)alquilo que contiene nitrógeno, y en donde cualquier grupo heterociclilo en Q⁸ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, (1-6C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (1-6C)alcoxi,

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amino, (1-6C)alquilamino y di-[(1-6C)alquil] amino,

y en donde cualquier grupo heterociclilo en Q¹ lleva opcionalmente 1 ó 2 sustituyentes oxo;

(mmm) Q¹ se selecciona de (3-7C)cicloalquilo, el cual se sustituye por 1 sustituyente seleccionado de, amino, (1-6C)alquilamino, di-[(1-6C)alquil]amino, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, y de un grupo de la fórmula:



en donde X⁵ es un enlace directo o se selecciona de O y N(R¹⁰), en donde R¹⁰ es hidrógeno o (1-6C)alquilo, y Q⁸ es heterociclilo que contiene nitrógeno o heterociclil-(1-6C)alquilo que contiene nitrógeno, y en donde cualquier grupo heterociclilo en Q⁸ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de hidroxil, (1-4C)alquilo, amino, (1-4C)alquilamino y di-[(1-4C)alquil]amino,

y en donde cualquier grupo heterociclilo en Q¹ lleva opcionalmente 1 ó 2 sustituyentes oxo;

(nnn) Z es O y Q¹ es (3-7C)cicloalquilo sustituido por 1 sustituyente seleccionado de, amino, (1-4C)alquilamino, di-[(1-4C)alquil]amino, amino-(1-4C)alquilo, (1-4C)alquilamino-Q⁴C)alquilo, di-[(1-4C)alquil]amino-(1-4C)alquilo, y de un grupo de la fórmula:



en donde X⁵ es un enlace directo, y Q⁶ es un heterociclilo que contiene nitrógeno de 5 ó 6 miembros, y en donde Q⁸ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de metilo, etilo, amino, metilamino, etilo o dimetilamino,

y en donde cualquier grupo heterociclilo en Q¹ lleva opcionalmente 1 sustituyente oxo;

(ooo) Z es O y Q¹ se selecciona de ciclopentilo y ciclohexilo, el cual se sustituye por un sustituyente seleccionado de pirrolidin-1-ilo, morfolino, piperidino y piperazin-1-ilo, y en donde cualquier grupo pirrolidinilo, morfolino, piperidino o piperazinilo en Q¹ lleva opcionalmente 1 ó 2 sustituyentes seleccionados de metilo, amino, metilamino, etilamino y

dimetilamino, y en donde cualquier grupo heterociclilo en Q^1 lleva opcionalmente un sustituyente oxo;

(ppp) Z es O y Q^1 es 4-(piperazin-1-il)ciclohexilo, en donde el grupo piperazin-1-ilo se sustituye opcionalmente en la posición 4 por (1-3C)alquilo, por ejemplo metilo;

(qqq) Z es O y Q^1 se selecciona de piperidin-4-ilo opcionalmente sustituido en la posición 1 por un sustituyente seleccionado de metilo, etilo, alilo, acetilo, metoxycarbonilmetilo, metoximetilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo y acetilmetilo,

y en donde el grupo piperidin-4-ilo lleva opcionalmente un sustituyente oxo;

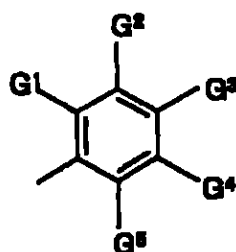
(rrr) Q^1Z es 1-metilpiperidin-4-iloxi;

(sss) Q^1Z es tetrahydrofuran-3-iloxi;

(ttt) Q^1Z es tetrahidropiran-4-iloxi;

(uuu) L es un enlace directo;

(vvv) Q^2 es un grupo arilo de fórmula Ia



Ia

en donde G^1 y G^5 son hidrógeno,

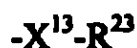
G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, (1-6C)alquilo, (2-8C)alquenilo y (2-8C)alquinilo,

G^3 se selecciona de hidrógeno, halógeno, hidroxilo, (1-6C)alquilo, (2-8C)alquenilo y (2-8C)alquinilo, o de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO_2 , $N(R^{20})$, CO, $C(R^{20})_2N(R^{20})$ y $N(R^{20})C(R^{20})_2$, en donde R^{20} es hidrógeno o (1-6C)alquilo, y Q^{10} es arilo, aril-(1-6C)alquilo, heteroarilo o heteroaril-(1-6C)alquilo,

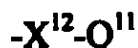
y en donde Q^{10} lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, formilo, carbamoilo, sulfamoilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^{13} es un enlace directo o se selecciona de O y N(R^{24}), en donde R^{24} es hidrógeno o (1-6C)alquilo, y R^{23} es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo, (2-6C)alcanoilo-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,
o G^3 y G^4 juntos forman un grupo de fórmula: -NH-CH=CH- ó -NH-N=CH-,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la porción heteroarilo del anillo bicíclico 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, ciano, (1-6C)alquilo y un grupo de la fórmula:



en donde X^{12} es un enlace directo o se selecciona de SO_2 , N(R^{21}), $SO_2N(R^{21})$ y CO, en donde R^{21} es hidrógeno o (1-6C)alquilo y Q^{11} es arilo,

aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, el cual lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, formilo, carbamoilo, sulfamoilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^{14} es un enlace directo o se selecciona de O y N(R^{26}), en donde R^{26} es hidrógeno o (1-6C)alquilo, y R^{25} es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo, con la condición que G^2 , G^3 y G^4 no son todos hidrógeno; (www) Q^2 es un grupo arilo de fórmula Ia como se define arriba en el texto, en donde G^1 , G^2 y G^5 son hidrógeno,

G^3 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, hidroxilo, (1-6C)alquilo, (2-8C)alquenilo y (2-8C)alquinilo,

con la condición que ambos G^3 y G^4 no son hidrógeno;

(xxx) Q^2 es un grupo arilo de fórmula Ia como se define arriba en el texto, en donde G^1 , G^2 , G^3 y G^5 son hidrógeno, y

G^4 se selecciona de cloro, bromo, metilo y etinilo,

(yyy) Q^2 es un grupo arilo de fórmula Ia como se define arriba en el texto, en donde G^1 , G^2 y G^5 son hidrógeno,

G^3 se selecciona de halógeno e hidroxilo, y

G^4 es halógeno;

(zzz) Q^2 es un grupo arilo de fórmula Ia como se define arriba en el texto, en donde G^1 , G^2 y G^3 son hidrógeno,

G^3 se selecciona de fluoro e hidroxilo, y

G^4 es cloro;

(aaaa) el grupo $Q^2LN(R^3)$ se selecciona de 3-cloro-4-fluoroanilino, 3-cloro-4-hidroxianilino, 3-fluoroanilino, 3-bromoanilino, 3-cloroanilino, 3-metilanilino y 3-etilanilino;

(bbbb) el grupo $Q^2LN(R^3)$ es 3-cloro-4-fluoroanilino;

(cccc) el grupo $Q^2LN(R^3)$ es 3-bromoanilino;

(dddd) el grupo $Q^2LN(R^3)$ es 3-cloroanilino;

(eeee) el grupo $Q^2LN(R^3)$ es 3-metilanilino;

(ffff) el grupo $Q^2LN(R^3)$ es 3-etilanilino;

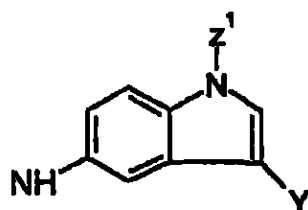
(gggg) Q^2 es un grupo arilo de fórmula Ia en donde:

G^1 , G^2 y G^3 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-NH-CH=CH-$ ó $-NH-N=CH-$,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la porción heteroarilo del anillo bicíclico 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, ciano y (1-6C)alquilo;

(hhhh) $Q^2LN(R^3)$ es un grupo de la fórmula Ic:

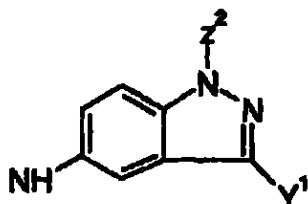


Ic

en donde Z^1 es hidrógeno o (1-4C)alquilo, y

Y se selecciona de hidrógeno, halógeno, (1-4C)alquilo y ciano;

(iiii) $Q^2LN(R^3)$ es un grupo de la fórmula Id:



Id

en donde Z^2 es hidrógeno o (1-4C)alquilo, y

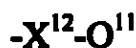
Y^1 se selecciona de hidrógeno y halógeno;

(iii) $Q^2LN(R^3)$ es un grupo de la fórmula Ic como se define arriba en el texto en donde Z^1 es hidrógeno y Y^1 se selecciona de cloro y bromo;

(kkkk) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^3 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-NH-CH=CH-$, y el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye en la posición 1 por un grupo de la fórmula:

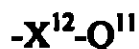


en donde X^{12} es un enlace directo y Q^{11} es fenil-(1-6C)alquilo o heteroaril-(1-6C)alquilo, y en donde cualquier grupo fenilo o heteroarilo en Q^{11} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, ciano, hidroxilo, amino, carbamoilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo y N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo, y en donde el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye opcionalmente en la posición 3 por un sustituyente seleccionado de halógeno, ciano y (1-6C)alquilo;

(llll) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^3 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-\text{NH}-\text{CH}=\text{CH}-$, y el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye en la posición 1 por un grupo de la fórmula:



en donde X^{12} es un enlace directo y Q^{11} es bencilo o heteroaril-metilo, y en donde cualquier grupo fenilo o heteroarilo en Q^{11} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, ciano, hidroxilo, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, y

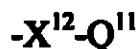
y en donde el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye opcionalmente en la posición 3 por halógeno;

y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;

(mmmm) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-\text{NH}-\text{CH}=\text{CH}-$, y el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye en la posición 1 por un grupo de la fórmula:



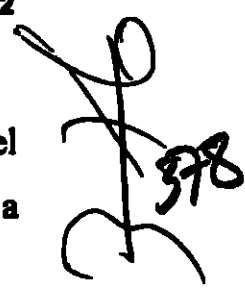
en donde X^{12} es un enlace directo y Q^{11} es bencilo el cual se sustituye opcionalmente por 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, metilo y etilo, (por ejemplo Q^{11} es 2-fluorobencilo o 3-fluorobencilo), y

y en donde el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye opcionalmente en la posición 3 por un sustituyente seleccionado de cloro y bromo;

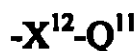
y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;

(nnnn) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno, y



G^3 y G^4 juntos forman un grupo de la fórmula: $-NH-CH=CH-$, y el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye en la posición 1 por un grupo de la fórmula:



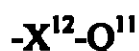
en donde X^{12} es un enlace directo y Q^{11} furfurilo, 3-furilmetilo, 2-oxazolilmetilo, 4-oxazolilmetilo, 3-isoxazolilmetilo, 5-isoxazolilmetilo, 2-imidazolilmetilo, 4-imidazolilmetilo, 2-, 3- or 4-piridilmetilo, 2-, 4- o 5-pirimidinilmetilo, 1,2,4-triazol-5-ilmetilo, 1,2,4-triazol-3-ilmetilo, 1,2,4-triazol-5-ilmetilo, 2-tienilmetilo, 3-tienilmetilo, 2-tiazolilmetilo, 4-tiazolilmetilo, 1,2,5-tiadiazol-3-ilmetilo, y en donde cualquier grupo heteroarilo en Q^{11} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, y en donde el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye opcionalmente en la posición 3 por halógeno;

y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;

(oooo) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-NH-CH=CH-$, y el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye en la posición 1 por un grupo de la fórmula:



en donde X^{12} es un enlace directo y Q^{11} es 2-oxazolilmetilo, 4-oxazolilmetilo, 3-isoxazolilmetilo, 5-isoxazolilmetilo, 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 2-tiazolilmetilo o 4-tiazolilmetilo y en donde cualquier grupo heteroarilo en Q^{11} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de amino, metilo, etilo, metilamino y dimetilamino;

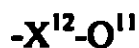
y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;



(pppp) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-NH-CH=CH-$, y el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye en la posición 1 por un grupo de la fórmula:



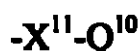
en donde X^{12} es un enlace directo y Q^{11} es 3-isoxazolilmetilo, 4-tiazolilmetilo o 2-piridilmetilo, y en donde cualquier grupo heteroarilo en Q^{11} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de metilo y etilo; y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;

(qqqq) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno,

G^4 se selecciona de hidrógeno, halógeno, (1-6C)alquilo, (1-6C)alcoxi, (2-6C)alquenilo y (2-6C)alquinilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} se selecciona de fenil-(1-6C)alquilo y heteroaril-(1-6C)alquilo, y en donde cualquier grupo fenilo o heteroarilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, ciano, hidroxilo, amino, carbamoilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo y N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo;

y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;



(rrrr) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^3 son hidrógeno,

G^4 se selecciona de hidrógeno, halógeno, (1-6C)alquilo y (2-6C)alquinilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} se selecciona de bencilo y heteroaril-metilo, y en donde cualquier grupo fenilo o heteroarilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de seleccionado de halógeno, hidroxilo, ciano, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, carbamoilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di[(1-6C)alquil]amino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo y N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo;

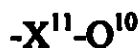
y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;

(ssss) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^3 son hidrógeno,

G^4 se selecciona de hidrógeno, fluoro, cloro, metilo y etinilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} es bencil cual se sustituye opcionalmente por 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, ciano y (1-4C)alquilo;

y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;

(tttt) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^3 son hidrógeno,

G^4 se selecciona de hidrógeno, cloro, metilo y etinilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} es bencil cual se sustituye opcionalmente por 1 sustituyente seleccionado de fluoro y Ciano (por ejemplo Q^{10} es bencilo o 3-fluorobencilo);

y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;

(uuuu) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno,

G^4 se selecciona de hidrógeno, cloro, metilo y etinilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} se selecciona de furfurilo, 3-furilmetilo, 2- ó 3-tienilmetilo, 2-, 4- ó 5-oxazolilmetilo, 3-, 4- ó 5-isoxazolilmetilo, 2-, 4- ó 5-1H-imidazolilmetilo, 2-, 4- ó 5-tiazolilmetilo, 3- ó 5-(1H-1,2,4-triazolil)metilo, 3- ó 4-(1,2,5-tiadiazolil)metilo, 2-, 3- ó 4-piridilmetilo y 2-, 4- ó 5-pirimidinilmetilo, y en donde el grupo heteroarilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino;

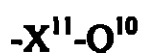
y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí;

(vvvv) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno,

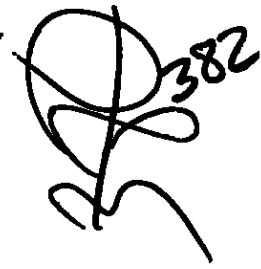
G^4 se selecciona de hidrógeno, cloro, metilo y etinilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} se selecciona de isoxazolilmetilo, tiazolilmetilo y piridilmetilo, y en donde el grupo heteroarilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de hidroxilo, amino, metilo, metilamino y di-metilamino;

y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene



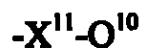
cualquiera de los significados definidos aquí; y

(www) Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno,

G^4 se selecciona de cloro y metilo, y

G^3 es un grupo de la fórmula:



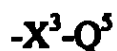
en donde X^{11} es O y Q^{10} se selecciona de 3-isoxazolilmetilo y 4-tiazolilmetilo, y en donde el grupo heteroarilo en Q^{10} lleva opcionalmente 1 sustituyente seleccionado de metilo y etilo (por ejemplo Q^{10} es 5-metil-isoxazol-3-ilmetilo, ó 4-tiazolil); y en donde m es 1, R^1 se localiza en la posición 7 y en donde R^1 tiene cualquiera de los significados definidos aquí.

Una incorporación particular de la presente invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó m es 1 y el grupo R^1 , cuando está presente, se selecciona de hidroxi, amino, metilo, etilo, propilo, butilo, pentilo, metoxi, etoxi, propoxi, butoxi, pentoxi, metilamino, etilamino, propilamino, dimetilamino, dietilamino, propilmetilamino, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido, propiolamido, pirrolidin-lilo, piperidino, homopiperidín-1-ilo, morfolino, tiamorfolino, piperazin-1-ilo y homopiperazin-1-ilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, $N(CH_3)$, CO, CONH y NHCO,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxi, amino, metoxi, metilsulfonilo, metilamino, y dimetilamino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O, NH y $N(CH_3)$ y Q^5 se selecciona de pirrolidin-1-ilo, pirrolidin-2-ilo, pirrolidin-3-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, homopiperidín-1-ilo, piperazin-

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1-il homopiperazin-1-ilo, fenilo, 2-, 3- ó 4-piridilo y 2-, 4- ó 5-pirimidinilo, y en donde cualquier grupo fenilo, piridilo, pirimidinilo o heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, metilo, etilo, n-propilo, isopropilo, metoxi, etoxi, 2-metoxietoxi, 2-hidroxietoxi, 3-hidroxipropoxi, 3-metoxipropoxi, aminometoxi, 2-aminoetoxi, 3-aminopropoxi, metilaminometoxi, 2-metilaminoetoxi, 2-etilaminoetoxi, dimetilaminometoxi, 2-dimetilaminoetoxi, amino, metilamino, dimetilamino, y en donde cualquier fracción pirrolidinilo, piperidinilo, piperazinilo, homopiperidinilo u homopiperazinilo en R¹ se sustituye además en forma opcional en un átomo de nitrógeno disponible con un sustituyente seleccionado de tetrahidrofurfurilo, tetrahidrofuran-3-ilmetilo, 1-metilpiperidin-4-ilo 1-etilpiperidin-4-ilo, 1-metilpiperidin-3-ilo 1-etilpiperidin-3-ilo y 2-morfolinoetilo, y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes oxo;

el grupo Q¹-Z- se selecciona de ciclopentilo, ciclohexilo, fenilo, bencilo, tetrahidrofuran-3-ilo, tetrahidropiran-3-ilo, tetrahidropiran-4-ilo, tetrahidrotiopiran-3-ilo, 1-oxotetrahidrotiopiran-3 -ilo, 1,1 -dioxotetrahidrotiopiran-3-ilo, tetrahidrotiopiran-4-ilo, 1-oxotetrahidrotiopiran-4-ilo, 1,1-dioxotetrahidrotiopiran-4-ilo, tetrahidrotien-3-ilo, 1,1-dioxotetrahidrotien-3-ilo, 1-oxotetrahidrotien-3-ilo, 2-imidazol-1-iletoxi, 2-(1,2,4-triazol-1-il)etoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-ilo, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-ilo, piperidin-4-ilo, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, homopiperidin-3-ilo, homopiperidin-4-ilo, homopiperidin-3-ilmetoxi, 2-piperazin-1-

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iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH_2 ó CH_3 en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

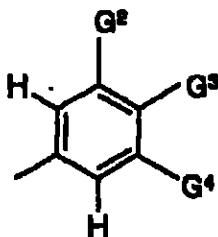
y en donde cualquier grupo fenilo o heterociclilo en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, metilo, etilo y metoxi,

y en donde cualquier grupo heterociclilo en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente 1 ó 2 sustituyentes oxo;

R^3 es hidrógeno;

L es un enlace directo; y

Q^2 es un grupo arilo de fórmula Ib



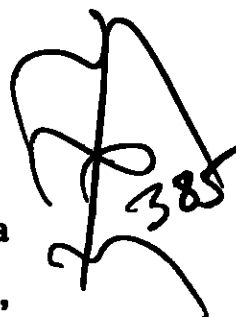
Ib

en donde cada uno de G^2 , G^3 y G^4 , que pueden ser los mismos o diferentes, se seleccionan de hidrógeno, fluoro, cloro, bromo, trifluorometilo, ciano, hidroxilo, metilo, etilo y etinilo, a condición que por lo menos uno de G^2 , G^3 y G^4 es distinto de hidrógeno,

o G^3 y G^4 juntos forman un grupo de fórmula: - -CH=CH-NH- , - -NH-CH=CH- , - -NH-N=CH- ó - -CH=N-NH- , - -S-N=CH- ó - -CH=N-S- , y el anillo heteroarilo bicíclico de 9 miembros así formado lleva opcionalmente en la porción heteroarilo del anillo bicíclico 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, trifluorometilo, ciano, hidroxilo, metilo y etilo;

o una sal de adición de ácido farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de



quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y se selecciona de hidroxilo, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH y $N(CH_3)$,

y en donde cualquier grupo terminal CH_3 en una cadena (1-6C)alcoxi en un sustituyente R^1 lleva opcionalmente en dicho grupo terminal CH_3 un sustituyente seleccionado de hidroxilo, amino y N-(1-metilpirrolidin-3-il)-N-metilamino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R^1 lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en un sustituyente R^1 lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahydrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo;

el grupo Q^1 -Z- se selecciona de ciclopentiloxi, tetrahydrofuran-3-iloxi, tetrahydropiran-4-iloxi, tetrahydrotiopiran-4-iloxi, 1, 1-dioxotetrahydrotiopiran-4-iloxi, 1-oxotetrahydrotiopiran-4-iloxi, tetrahydrotien-3-iloxi, 1,1-dioxotetrahydrotien-3-iloxi, 1-oxotetrahydrotien-3-iloxi, pirrolidin-3-iloxi, pirrolidin-2-iloxi, piperidin-3-iloxi, piperidin-4-iloxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi y azetidin-3-iloxi,

y en donde el grupo azetidinilo, pirrolidinilo, piperidinilo u homopiperidinilo en el grupo Q^1 -Z- es opcionalmente N- sustituido por un

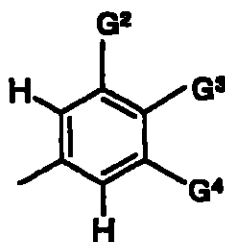
sustituyente seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, tert-butilo, alilo, 2-propinilo, acetilo, propionilo, metoxycarbonilo, etoxycarbonilo, propoxycarbonilo, tert-butoxycarbonilo, metilsulfonilo, etilsulfonilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-dimetilcarbamoil)etilo, acetilmetilo, 2-acetiletilo, metoxycarbonilmetilo y 2-metoxycarboniletilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

R³ es hidrógeno;

L es un enlace directo; y

Q² es un grupo arilo de fórmula Ib



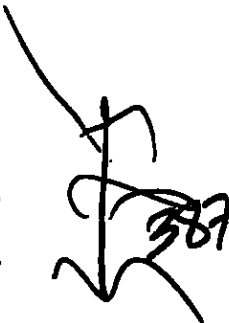
Ib

en donde G² es hidrógeno, y G³ y G⁴, que pueden ser los mismos o diferentes, se seleccionan de hidrógeno, fluoro, cloro, bromo, ciano, hidroxilo, metilo, etilo, y etinilo, a condición que por lo menos uno de G³ y G⁴ es distinto de hidrógeno,

o G³ y G⁴ juntos forman un grupo de fórmula: -CH=CH-NH-, -NH-CH=CH-, -NH-N=CH-, -CH=N-NH-, y el anillo heteroarilo bicíclico de 9 miembros así formado lleva opcionalmente en la porción heteroarilo del anillo bicíclico 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, y metilo; o una sal de adición de ácido farmacéuticamente aceptable del mismo.

Una incorporación más de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R¹, cuando está presente, se localiza en la posición 7 y se selecciona de metoxi, 2-metoxietoxi, 3-(R)-

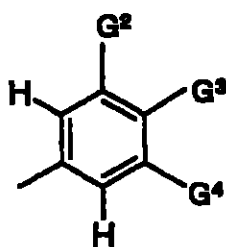


dimetilaminopirrolidin-1-ilo, 1-metilpiperidin-4-ilmetoxi, 3-(N-(2-hidroxietil)-N-metilamino)propoxi, 2-(N-(2-metoxietil)-N-metilamino)etoxi, 2-(N-(2-hidroxietil)-N-metilamino)etoxi, 3-(N-(2-dimetilaminoetil)-N-metilamino)propoxi, 2-(N-(2-dimetilaminoetil)-N-metilamino)etoxi, 3-pirrolidin-1-ilpropoxi, 3-(3-hidroxipirrolidin-1-il)propoxi, 2-pirrolidin-1-iletoxi, 2-(3-hidroxipirrolidin-1-il)etoxi, 2-(3-dimetilaminopirrolidin-1-il)etoxi, 3-(3-dimetilaminopirrolidin-1-il)propoxi, 3-(N-metil-N-(1-metilpirrolidin-3-il)amino)propoxi, 2-(N-metil-N-(1-metilpirrolidin-3-il)amino)etoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 3-(4-metilpiperazin-1-il)propoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-isopropilpiperazin-1-il)propoxi, 2-(4-isopropilpiperazin-1-il)etoxi, 3-(4-(2-metoxietil)piperazin-1-il)propoxi, 2-(4-(2-metoxietil)piperazin-1-il)etoxi, 2-(4-(2-morfolinoetil)piperazin-1-il)etoxi, 3-(4-(2-morfolinoetil)piperazin-1-il)propoxi, 2-(4-tetrahidrofurfuril)piperazin-1-iletoxi, 3-(4-tetrahidrofurfuril)piperazin-1-ilpropoxi, 2-(4-(1-metilpiperidin-4-il)piperazin-1-iletoxi, 3-(4-(1-metilpiperidin-4-il)piperazin-1-ilpropoxi, 2-(4-metilhomopiperazin-1-il)etoxi, 3-(4-metilhomopiperazin-1-il)propoxi, el grupo Q¹-Z- se selecciona de ciclopentiloxi, 1-metilazetidin-3-iloxi, 1-isopropilazetidin-3-iloxi, tetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, tetrahidrofuran-3-iloxi, 1-metilpirrolidin-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, piperidin-4-iloxi, 1-metilpiperidin-4-iloxi, 1-etilpiperidin-4-iloxi, 1-propilpiperidin-4-iloxi, 1-(2-metoxietil)piperidin-4-iloxi, 1-acetilpiperidin-4-iloxi, 1-acetilmetilpiperidin-4-iloxi, 1-alilpiperidin-4-iloxi, 1-(2-propinil)piperidin-4-iloxi, 1-metoxycarbonilmetilpiperidin-4-iloxi, 1-carbamoilmetilpiperidin-4-iloxi y 1-metanosulfonilpiperidin-4-iloxi;

R³ es hidrógeno;

L es un enlace directo o CH(CH₃); y

Q² es un grupo arilo de fórmula Ib

Ib

en donde G^2 es hidrógeno, y G^3 y G^4 , que pueden ser los mismos o diferentes, se seleccionan de hidrógeno, fluoro, cloro, bromo, hidroxilo, metilo y etinilo, a condición que cuando L es un enlace directo, por lo menos uno de G^3 y G^4 es distinto de hidrógeno,

o G^3 y G^4 juntos forman un grupo de fórmula: - $CH=CH-NH-$, $-NH-CH=CH-$, $-NH-N=CH-$, $-CH=N-NH-$, $-S-N=CH-$ ó $-CH=N-S-$ y el anillo heteroarilo bicíclico de 9 miembros así formado lleva opcionalmente en un átomo de carbono en la porción heteroarilo del anillo bicíclico 1 sustituyente seleccionado de fluoro, cloro, bromo, ciano, y metilo;

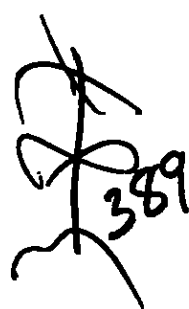
o una sal de adición de ácido farmacéuticamente aceptable del mismo.

Grupos apropiados de la Fórmula 1b en esta incorporación incluyen, por ejemplo, 3-bromofenilo, 3-clorofenilo, 3-fluorofenilo, 3-metilfenilo, 3-etinilfenilo, 3-cloro-4-hidroxifenilo, 3-cloro-4-fluorofenilo, indol-5-ilo, 3-bromoindol-5-ilo, 3-cloroindol-5-ilo, 3-cianoindol-5-ilo, 3-metilindol-5-ilo, 3-cloroindol-5-il indazol-5-ilo, 3-bromoindazol-5-ilo, 3-cloroindazol-5-ilo, benzisotiazol-5-ilo y 3-metil-benzisotiazol-5-ilo;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde m es 0 ó m es 1 y el grupo R^1 , cuando está presente, se selecciona de hidroxilo, amino, metilo, etilo, propilo, butilo, pentilo, metoxi, etoxi, propoxi, butoxi, pentoxi, metilamino, etilamino, propilamino, dimetilamino, dietilamino, N-propil-N-metilamino, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido, propiolamido, pirrolidin-1-ilo, piperidino, homopiperidin-1-ilo, morfolino, tiamorfolino, piperazin-1-ilo y homopiperazin-1-ilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-



6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, $N(CH_3)$, CO, CONH y NHCO,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxilo, metilsulfonilo, metilamino, y dimetilamino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O, NH y $N(CH_3)$ y Q^5 se selecciona de pirrolidin-1-ilo, pirrolidin-2-ilo, pirrolidin-3-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-1-ilo, piperazin-1-il homopiperazin-1-ilo, fenilo, (2-, 3- ó 4-)piridilo y (2-, 4- ó 5-)pirimidinilo,

y en donde cualquier grupo fenilo, piridilo, pirimidinilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, metilo, etilo, n-propilo, isopropilo, metoxilo, etoxilo, 2-metoxietoxilo, 2-hidroxietoxilo, 3-hidroxipropoxilo, 3-metoxipropoxilo, aminometoxilo, 2-aminoetoxilo, 3-aminopropoxilo, metilaminometoxilo, 2-metilaminoetoxilo, 2-etilaminoetoxilo, dimetilaminometoxilo, 2-dimetilaminoetoxilo, amino, metilamino, dimetilamino, y en donde cualquier fracción pirrolidinilo, piperidinilo, piperazinilo, homopiperidinilo u homopiperazinilo en R^1 se sustituye además en forma opcional en un átomo de nitrógeno disponible con un sustituyente seleccionado de tetrahidrofurfurilo, tetrahidrofuran-3-ilmetilo, 1-metilpiperidin-4-il 1-etilpiperidin-4-ilo, 1-metilpiperidin-3-il 1-etilpiperidin-3-ilo y 2-morfolinoetilo, y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

el grupo Q^1-Z se selecciona de ciclopentiloxilo, ciclohexiloxilo, fenoxilo, benciloxilo, tetrahidrofuran-3-iloxilo, tetrahidropiran-3-iloxilo, tetrahidropiran-4-iloxilo, tetrahidrotiopiran-3-iloxilo, 1-oxotetrahidrotiopiran-3-

iloxi, 1,1-dioxotetrahidrotiopiran-3-iloxi, tetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, tetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, 2-imidazol-1-iletoxi, 2-(1,2,4-triazol-1-il)etoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi, homopiperidin-3-ilmetoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH_2 ó CH_3 en el grupo $\text{Q}^1\text{-Z}$ lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

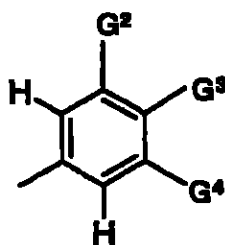
y en donde cualquier grupo fenilo o heterociclilo en el grupo $\text{Q}^1\text{-Z}$ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, metilo, etilo y metoxi,

y en donde cualquier grupo heterociclilo en el grupo $\text{Q}^1\text{-Z}$ lleva opcionalmente 1 ó 2 sustituyentes oxo;

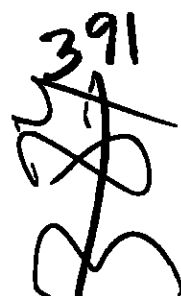
R^3 es hidrógeno;

L es un enlace directo; y

Q^2 es un grupo arilo de fórmula Ib

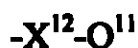


Ib

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en donde G^3 y G^4 juntos forman un grupo de fórmula: - $\text{CH}=\text{CH}-\text{NH}-$,
- $\text{NH}-\text{CH}=\text{CH}-$, - $\text{NH}-\text{N}=\text{CH}-$ ó - $\text{CH}=\text{N}-\text{NH}-$,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo seleccionado de trifluorometilo, (1-4C)alquilo, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo, (1-4C)alcoxicarbonilo, carbamoilo, N-(1-4C)alquilcarbamoilo, N,N-di-(1-4C)alquilcarbamoilo y (1-4C)alquilsulfonilo, o de un grupo de la fórmula:



en donde X^{12} es un enlace directo o se selecciona de SO_2 y CO , en donde R^{21} es hidrógeno o (1-6C)alquilo y Q^{11} es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, el cual lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de ciano, halógeno, hidroxilo, (1-6C)alquilo y (1-6C)alcoxi,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en un átomo de carbono disponible en la porción heteroarilo del anillo bicíclico 1 sustituyente seleccionado de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, (1-6C)alquilo, (2-6C)alquenilo, (2-6C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, y cualquier anillo heteroarilo bicíclico así formado lleva opcionalmente 1 ó 2 grupos oxo o tioxo,

y G^2 se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino; o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y se selecciona de hidroxilo, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-



piperazin-1-iletoxi, 3 -piperazin-1-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH y N(CH₃),

y en donde cualquier grupo terminal CH₃ en una cadena (1-6C)alcoxi en un sustituyente R¹ lleva opcionalmente en el grupo terminal CH₃ un sustituyente seleccionado de hidroxilo, amino y N-(1-metilpirrolidin-3-il)-N-metilamino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R¹ lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en un sustituyente R¹ lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahidrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo;

el grupo Q¹-Z- se selecciona de ciclopentiloxi, tetrahydrofuran-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi, tetrahidrotien-3-iloxi, 1,1-dioxodotetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, pirrolidin-3-iloxi, pirrolidin-2-iloxi, piperidin-3-iloxi, piperidin-4-iloxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi y azetidín-3-iloxi,

y en donde el grupo azetidínilo, pirrolidinilo, piperidinilo u homopiperidinilo en el grupo Q¹-Z- es opcionalmente N- sustituido por un sustituyente seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, tert-butilo, alilo, 2-propinilo, acetilo, propionilo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, tert-butoxicarbonilo, metilsulfonilo, etilsulfonilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-dimetilcarbamoil)etilo, acetilmetilo, 2-

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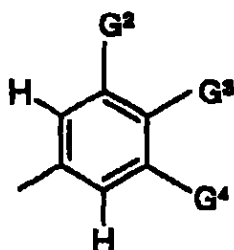
acetiletilo, metoxycarbonilmetilo y 2-metoxycarboniletilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

R³ es hidrógeno;

L es un enlace directo; y

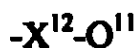
Q² es un grupo arilo de fórmula Ib



Ib

en donde G³ y G⁴ juntos forman un grupo de fórmula: -CH=CH-NH-, -NH-CH=CH-, -NH-N=CH- ó -CH=N-NH-,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G³ y G⁴ se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo de la fórmula:



en donde X¹² es un enlace directo o se selecciona de SO₂ y CO, en donde Q¹¹ es fenilo, bencilo, 2-feniletilo, 2-furilo, furfurilo, 3-furilo, 3-furilmetilo, 2-oxazolilo, 4-oxazolilo, 2-oxazolilmetilo, 4-oxazolilmetilo, 2-imidazolilo, 4-imidazolilo, 2-imidazolilmetilo, 4-imidazolilmetilo, 2-, 3- ó 4-piridilo, 2-, 3- ó 4-piridilmetilo, 2-(2-, 3- ó 4-piridil)etilo, 2-, 4- ó 5-pirimidinilo, 2-, 4- ó 5-pirimidinilmetilo, 2-(2-, 4- ó 5-pirimidinil)etilo, 1,2,4-triazol-3-ilo, 1,2,4-triazol-5-ilmetilo, triazol-3-ilmetilo, 1,2,4-triazol-5-ilo, 2-tienilo, 3-tienilo, 2-tienilmetilo, 3-tienilmetilo, 2-(2-tienil)etilo, 2-(3-tienil)etilo, 2-tiazolilo, 4-tiazolilo, 2-tiazolilmetilo, 4-tiazolilmetilo, 1,2,5-tiadiazol-3-ilo, 1,2,5-tiadiazol-3-ilmetilo, 2-(1,2,5-tiadiazol-3-il)etilo el cual lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, hidroxil, metilo y etilo,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G³ y G⁴ juntos se enlazan lleva opcionalmente en un átomo de carbono

disponible en la porción heteroarilo del anillo bicíclico 1 sustituyente seleccionado de fluoro, cloro, bromo, ciano, hidroxilo, amino, metilo, etilo, vinilo, etinilo, metilamino y di-metilamino,

y G^2 se selecciona de hidrógeno, fluoro, cloro, bromo, trifluorometilo, ciano, hidroxilo, amino, metilo, etilo, vinilo, etinilo, metilamino y dimetilamino; o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde m es 0 ó 1 y el grupo¹, cuando está presente, se localiza en la posición 7 y es metoxi,

Q^1 -Z- es 1-metilpiperidin-1-iloxi,

R^3 es hidrógeno;

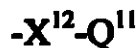
L es un enlace directo; y

Q^2 es un grupo arilo de fórmula Ib como se define arriba en el texto en donde,

G^2 es hidrógeno,

y G^3 y G^4 juntos forman un grupo de fórmula: -NH-CH=CH- ó -NH-N=CH-,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo de la fórmula:

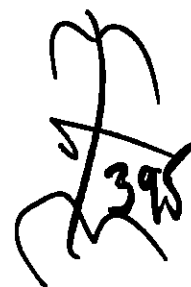


en donde X^{12} es un enlace directo o es SO_2 , y Q^{11} es fenilo, bencilo, ó 2-piridilmetilo el cual lleva opcionalmente un sustituyente fluoro,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la posición 3 un sustituyente cloro; o una sal farmacéuticamente aceptable del mismo.

Valores apropiados para Q^2 es esta incorporación incluyen, por ejemplo 1-bencenosulfonilindol-5-ilo, 1-bencilindol-5-ilo, 1-(2-piridilmetil)indol-5-ilo, 1-(2-piridilmetil)indazol-5-ilo y 1-(3-fluorobencil)indazol-5-ilo.

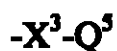
Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde m es 0 ó m es 1 y el grupo R^1 ,



cuando está presente, se selecciona de hidroxilo, amino, metilo, etilo, propilo, butilo, pentilo, metoxi, etoxi, propoxi, butoxi, pentoxi, metilamino, etilamino, propilamino, dimetilamino, dietilamino, propilmetilamino, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido, propiolamido, pirrolidin-1-ilo, piperidino, homopiperidin-1-ilo, morfolino, tiamorfolino, piperazin-1-ilo y homopiperazin-1-ilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(CH₃), CO, CONH y NHCO,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R¹ lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino, y dimetilamino, o de un grupo de la fórmula:



en donde X³ es un enlace directo o se selecciona de O, NH y N(CH₃) y Q⁵ se selecciona de pirrolidin-1-ilo, pirrolidin-2-ilo, pirrolidin-3-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-1-ilo, piperazin-1-il homopiperazin-1-ilo, fenilo, 2-, 3- ó 4-piridilo y 2-, 4- ó 5-pirimidinilo,

y en donde cualquier grupo fenilo, piridilo, pirimidinilo o heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, metilo, etilo, n-propilo, isopropilo, metoxi, etoxi, 2-metoxietoxi, 2-hidroxietoxi, 3-hidroxipropoxi, 3-metoxipropoxi, aminometoxi, 2-aminoetoxi, 3-aminopropoxi, metilaminometoxi, 2-metilaminoetoxi, 2-etilaminoetoxi, dimetilaminometoxi, 2-dimetilaminoetoxi, amino, metilamino, dimetilamino, y en donde cualquier fracción pirrolidinilo, piperidinilo, piperazinilo, homopiperidinilo u homopiperazinilo en R¹ se sustituye además en forma opcional en un átomo de nitrógeno disponible con un sustituyente seleccionado de tetrahidrofurfurilo, tetrahidrofuran-3-ilmetilo, 1-metilpiperidin-4-il 1-

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etilpiperidin-4-ilo, 1-metilpiperidin-3-il 1-etilpiperidin-3-ilo y 2-morfolinoetilo, y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes oxo;

el grupo Q¹-Z- se selecciona de ciclopentiloxi, ciclohexiloxi, fenoxi, benciloxi, tetrahidrofuran-3-iloxi, tetrahidropiran-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-3-iloxi, 1-oxotetrahidrotiopiran-3-iloxi, 1,1-dioxotetrahidrotiopiran-3-iloxi, tetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, tetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, 2-imidazol-1-iletoxi, 2-(1,2,4-triazol-1-il)etoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi, homopiperidin-3-ilmetoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q¹-Z- lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

y en donde cualquier grupo fenilo o heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, metilo, etilo y metoxi,

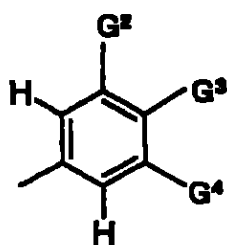
y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

R³ es hidrógeno;

L es un enlace directo; y

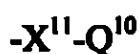
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Q^2 es un grupo arilo de fórmula Ib



Ib

en donde G^3 se selecciona de carbamoilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, o de un grupo de la fórmula:



en donde X^{11} es $CON(R^{20})$, en donde R^{20} es hidrógeno o (1-6C)alquilo, y Q^{10} es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde Q^{10} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, ciano, nitro, hidroxilo, amino, carbamoilo, metilo, etilo, vinilo, alilo, etinilo, metoxi, etoxi, metiltio, etiltio, metilsulfinilo, etilsulfinilo, metilsulfonilo, etilsulfonilo, metilamino, di-metilamino, metoxicarbonilo, etoxicarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetilo, propionilo, acetamido, propionamido, N-metilsulfamoilo, N,N-dimetilsulfamoilo, metanosulfonilamino y N-metil-metanosulfonilamino, y en donde cualquier grupo heterociclilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,

y G^2 y G^4 cada uno independientemente se seleccionan de hidrógeno, fluoro, cloro, trifluorometilo, ciano, nitro, hidroxilo, amino, metilo, etilo, vinilo, alilo, etinilo; o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde m es 0 ó m es 1 y el grupo R^1 , cuando está presente, se selecciona de hidroxilo, amino, metilo, etilo, propilo, butilo, pentilo, metoxi, etoxi, propoxi, butoxi, pentoxi, metilamino, etilamino,

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propilamino, dimetilamino, dietilamino, propilmetilamino, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido, propiolamido, pirrolidin-1-ilo, piperidino, homopiperidin-1-ilo, morfolino, tiamorfolino, piperazin-1-ilo y homopiperazin-1-ilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(CH₃), CO, CONH y NHCO,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino, y dimetilamino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O, NH y N(CH₃) y Q^5 se selecciona de pirrolidin-1-ilo, pirrolidin-2-ilo, pirrolidin-3-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-1-ilo, piperazin-1-il homopiperazin-1-ilo, fenilo, 2-, 3- ó 4-piridilo y 2-, 4- ó 5-pirimidinilo,

y en donde cualquier grupo fenilo, piridilo, pirimidinilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, metilo, etilo, n-propilo, isopropilo, metoxi, etoxi, 2-metoxietoxi, 2-hidroxietoxi, 3-hidroxipropoxi, 3-metoxipropoxi, aminometoxi, 2-aminoetoxi, 3-aminopropoxi, metilaminometoxi, 2-metilaminoetoxi, 2-etilaminoetoxi, dimetilaminometoxi, 2-dimetilaminoetoxi, amino, metilamino, dimetilamino, y en donde cualquier fracción pirrolidinilo, piperidinilo, piperazinilo, homopiperidinilo u homopiperazinil en R^1 se sustituye además en forma opcional en un átomo de nitrógeno disponible con un sustituyente seleccionado de tetrahidrofurfurilo, tetrahidrofuran-3-ilmetilo, 1-metilpiperidin-4-il 1-etilpiperidin-4-ilo, 1-metilpiperidin-3-il 1-etilpiperidin-3-ilo y 2-morfolinoetilo, y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2

sustituyentes oxo;

el grupo Q^1-Z se selecciona de ciclopentiloxi, ciclohexiloxi, fenoxi, benciloxi, tetrahydrofuran-3-iloxi, tetrahidropiran-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-3-iloxi, 1-oxotetrahidrotiopiran-3-iloxi, 1,1-dioxotetrahidrotiopiran-3-iloxi, tetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, tetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, 2-imidazol-1-iletoxi, 2-(1,2,4-triazol-1-il)etoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahydro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahydro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi, homopiperidin-3-ilmetoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH_2 ó CH_3 en el grupo Q^1-Z lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

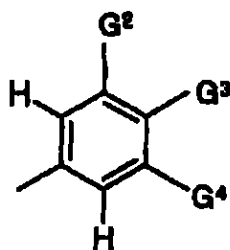
y en donde cualquier grupo fenilo o heterociclilo en el grupo Q^1-Z lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, metilo, etilo y metoxi,

y en donde cualquier grupo heterociclilo en el grupo Q^1-Z lleva opcionalmente 1 ó 2 sustituyentes oxo;

R^3 es hidrógeno;

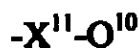
L es un enlace directo; y

Q^2 es un grupo arilo de fórmula Ib



Ib

en donde G^3 se selecciona de un grupo de la fórmula:



en donde X^{11} es CO y Q^{10} es un nitrógeno de 5 a 10 miembros que contiene un grupo heterocíclico enlazado a X^{11} por un átomo de nitrógeno,

y Q^{10} lleva opcionalmente 1 ó 2 sustituyentes seleccionado de halógeno, ciano, hidroxilo, amino, (1-6C)alquilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino, y G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y se selecciona de hidroxilo, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH y $N(CH_3)$,

y en donde cualquier grupo terminal CH_3 en una cadena (1-6C)alcoxi en un sustituyente R^1 lleva opcionalmente en el grupo terminal CH_3 un

sustituyente seleccionado de hidroxilo, amino y 1-metilpirrolidin-3-il(metil)amino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R¹ lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en un sustituyente R¹ lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahydrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo;

el grupo Q¹-Z- se selecciona de ciclopentilo, tetrahydrofuran-3-ilo, tetrahydropiran-4-ilo, tetrahydrotiopiran-4-ilo, 1,1-dioxotetrahydrotiopiran-4-ilo, 1-oxotetrahydrotiopiran-4-ilo, tetrahydrotien-3-ilo, 1,1-dioxotetrahydrotien-3-ilo, 1-oxotetrahydrotien-3-ilo, pirrolidin-3-ilo, pirrolidin-2-ilo, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-3-ilo, homopiperidin-4-ilo y azetidín-3-ilo,

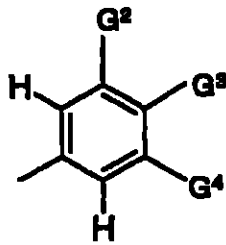
y en donde el grupo azetidínilo, pirrolidinilo, piperidinilo u homopiperidinilo en el grupo Q¹-Z- es opcionalmente N- sustituido por un sustituyente seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, tert-butilo, alilo, 2-propinilo, acetilo, propionilo, metoxycarbonilo, etoxycarbonilo, propoxycarbonilo, tert-butoxycarbonilo, metilsulfonilo, etilsulfonilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-dimetilcarbamoil)etilo, acetilmetilo, 2-acetiletilo, metoxycarbonilmetilo y 2-metoxycarboniletilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

R³ es hidrógeno;

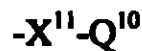
L es un enlace directo; y

Q² es un grupo arilo de fórmula Ib

Ib

en donde G^3 se selecciona de un grupo de la fórmula:



en donde X^{11} es CO y Q^{10} se selecciona de pirrolidin-1-ilo, piperidino, homopiperidino, morfolino, piperazin-1-ilo, homopiperazin-1-ilo, decahidroquinolin-1-ilo y decahidroisoquinolin-2-ilo,

y en donde Q^{10} lleva opcionalmente 1 ó 2 sustituyentes seleccionados de fluoro, cloro, bromo, ciano, hidroxilo, amino, metilo, etilo, metilamino y dimetilamino,

y G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, trifluorometilo, ciano, hidroxilo, amino, metilo, etilo, vinilo, etinilo, metilamino y di-metilamino;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y es metoxi,

El grupo Q^1-Z es 1-metilpiperidin-4-ilo,

R^3 es hidrógeno;

L es un enlace directo; y

Q^2 es un grupo arilo de fórmula Ib como se define arriba en el texto en donde en donde G^3 es un grupo de la fórmula:



en donde Q^{10} se selecciona de piperidino, homopiperidino, decahidroquinolin-1-ilo y decahidroisoquinolin-2-ilo, el cual se sustituye opcionalmente por metilo,

y G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, cloro y etinilo, o una sal farmacéuticamente aceptable del mismo.

Valores apropiados para Q^2 en esta incorporación incluyen por ejemplo 3-cloro-4-(homopiperidin-1-ilcarbonil)fenilo, 3-cloro-4-(decahidroquinolin-1-ilcarbonil)fenilo, 3-cloro-4-(decahidroisoquinolin-1-ilcarbonil)fenilo, 3-cloro-4-(3-metilpiperidin-1-ilcarbonil)fenilo, 3-cloro-4-(4-metilpiperidin-1-ilcarbonil)fenilo, 3-etinil-4-(decahidroquinolin-1-ilcarbonil)fenilo y 3-etinil-4-(decahidroquinolin-1-ilcarbonil)fenilo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde m es 0 ó m es 1 y el grupo R^1 , cuando está presente, se selecciona de hidroxilo, amino, metilo, etilo, propilo, butilo, pentilo, metoxi, etoxi, propoxi, butoxi, pentoxi, metilamino, etilamino, propilamino, dimetilamino, dietilamino, propilmetilamino, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido, propiolamido, pirrolidin-1-ilo, piperidino, homopiperidin-1-ilo, morfolino, tiamorfolino, piperazin-1-ilo y homopiperazin-1-ilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, $N(CH_3)$, CO, CONH y NHCO,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino, y dimetilamino, o de un grupo de la fórmula:



en donde X^3 es un enlace directo o se selecciona de O, NH y $N(CH_3)$ y Q^5 se selecciona de pirrolidin-1-ilo, pirrolidin-2-ilo, pirrolidin-3-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-1-ilo, piperazin-1-ilo homopiperazin-1-ilo, fenilo, 2-, 3- ó 4-piridilo y 2-, 4- ó 5-pirimidinilo,

y en donde cualquier grupo fenilo, piridilo, pirimidinilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2

sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, metilo, etilo, n-propilo, isopropilo, metoxi, etoxi, 2-metoxietoxi, 2-hidroxietoxi, 3-hidroxipropoxi, 3-metoxipropoxi, aminometoxi, 2-aminoetoxi, 3-aminopropoxi, metilaminometoxi, 2-metilaminoetoxi, 2-etilaminoetoxi, dimetilaminometoxi, 2-dimetilaminoetoxi, amino, metilamino, dimetilamino, y en donde cualquier fracción pirrolidinilo, piperidinilo, piperazinilo, homopiperidinilo u homopiperazinilo en R¹ se sustituye además en forma opcional en un átomo de nitrógeno disponible con un sustituyente seleccionado de tetrahydrofurfurilo, tetrahydrofuran-3-ilmetilo, 1-metilpiperidin-4-il 1-etilpiperidin-4-ilo, 1-metilpiperidin-3-ilo, 1-etilpiperidin-3-ilo y 2-morfolinoetilo, y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes oxo;

el grupo Q¹-Z- se selecciona de ciclopentiloxi, ciclohexiloxi, fenoxi, benciloxi, tetrahydrofuran-3-iloxi, tetrahydropiran-3-iloxi, tetrahydropiran-4-iloxi, tetrahydrotiopiran-3-iloxi, 1-oxotetrahydrotiopiran-3-iloxi, 1,1-dioxotetrahydrotiopiran-3-iloxi, tetrahydrotiopiran-4-iloxi, 1-oxotetrahydrotiopiran-4-iloxi, 1,1-dioxotetrahydrotiopiran-4-iloxi, tetrahydrotien-3-iloxi, 1,1-dioxotetrahydrotien-3-iloxi, 1-oxotetrahydrotien-3-iloxi, 2-imidazol-1-iletexi, 2-(1,2,4-triazol-1-il)etoxi, 2-pirrolidin-1-iletexi, 3-pirrolidin-1-ilpropoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletexi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahydro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahydro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletexi, piperidin-4-ilmetoxi, 2-piperidin-4-iletexi, 2-homopiperidin-1-iletexi, 3-homopiperidin-1-ilpropoxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi, homopiperidin-3-ilmetoxi, 2-piperazin-1-iletexi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletexi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q¹-Z- lleva

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opcionalmente en cada dicho grupo CH_2 ó CH_3 un sustituyente seleccionado de hidroxilo, amino, metoxi, metilsulfonilo, metilamino y dimetilamino,

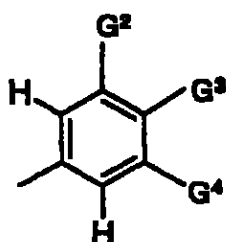
y en donde cualquier grupo fenilo o heterociclilo en el grupo $\text{Q}^1\text{-Z}$ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxilo, amino, metilo, etilo y metoxi,

y en donde cualquier grupo heterociclilo en el grupo $\text{Q}^1\text{-Z}$ lleva opcionalmente 1 ó 2 sustituyentes oxo;

R^3 es hidrógeno;

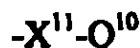
L es un enlace directo; y

Q^2 es un grupo arilo de fórmula Ib



Ib

en donde G^3 se selecciona de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO_2 , $\text{N}(\text{R}^{20})$, CO, $\text{CH}(\text{OR}^{20})$, $\text{C}(\text{R}^{20})_2\text{O}$, $\text{C}(\text{R}^{20})_2\text{NR}^{20}$, y $\text{C}(\text{R}^{20})_2\text{S}$, en donde R^{20} es hidrógeno, metilo o etilo, y Q^{10} es un grupo fenilo, bencilo, 2-feniletilo, naftilo, naftilmetilo ó 2-naftiletilo, el cual se sustituye opcionalmente con 1 ó 2 sustituyentes seleccionados de fluoro, cloro, bromo, trifluorometilo, nitro, metilo, etilo, isopropilo, vinilo, etinilo y ciano,

o Q^{10} es una fracción heteroarilo seleccionada de furilo, furilmetilo, 2-(furil)etilo, tienilo, tienilmetilo, 2-(tienil)etilo, oxazolilo, oxazolilmetilo, 2-(oxazolil)etilo, isoxazolilo, isoxazolilmetilo, 2-(isoxazolil)etilo, imidazolilo, imidazolilmetilo, 2-(imidazolil)etilo, tiazolilo, tiazolilmetilo, 2-(tiazolil)etilo, 1,2,4-triazolilo, 1,2,4-triazolilmetilo, 2-(1,2,4-triazolil)etilo, 1,2,5-tiadiazolilo, 1,2,5-tiadiazolilmetilo, 2-(1,2,5-tiadiazolil)etilo, piridilo, piridilmetilo, 2-(piridil)etilo, pirimidinilo, pirimidinilmetilo, 2-

(pirimidinil)etilo, 1,3-benzodioxolilo, 1,3-benzodioxolilmetilo, 2-(1,3-benzodioxolil)etilo, quinolinilo, quinolinilmetilo, 2-(quinolinil)etilo, isoquinolinilo, isoquinolinilmetilo, 2-(isoquinolinil)etilo, quinazolinilo, quinazolinilmetilo y 2-(quinazolinil)etilo, el cual se sustituye opcionalmente con uno o dos sustituyentes seleccionados de fluoro, cloro, bromo, nitro, metilo, trifluorometilo, etilo, isopropilo, metoxi y etoxi;

y cada uno de G^2 y G^4 independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, trifluorometilo, metilo, etilo, vinilo, alilo, etinilo, metilamino y di-metilamino;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y se selecciona de hidroxilo, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH y $N(CH_3)$,

y en donde cualquier grupo terminal CH_3 en una cadena (1-6C)alcoxi en un sustituyente R^1 lleva opcionalmente en el grupo terminal CH_3 un sustituyente seleccionado de hidroxilo, amino y N - (1-metilpirrolidin-3-il)- N -metilamino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R^1 lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en

un sustituyente R^1 lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahydrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo;

el grupo Q^1 -Z- se selecciona de ciclopentilo, tetrahydrofuran-3-ilo, tetrahidropiran-4-ilo, tetrahidrotiopiran-4-ilo, 1,1-dioxotetrahidrotiopiran-4-ilo, 1-oxotetrahidrotiopiran-4-ilo, tetrahidrotien-3-ilo, 1,1-dioxotetrahidrotien-3-ilo, 1-oxotetrahidrotien-3-ilo, pirrolidin-3-ilo, pirrolidin-2-ilo, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-3-ilo, homopiperidin-4-ilo y azetidin-3-ilo,

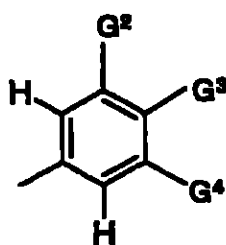
y en donde el grupo azetidinilo, pirrolidinilo, piperidinilo u homopiperidinilo en el grupo Q^1 -Z- es opcionalmente N-sustituido por un sustituyente seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, tert-butilo, alilo, 2-propinilo, acetilo, propionilo, metoxycarbonilo, etoxycarbonilo, propoxycarbonilo, tert-butoxycarbonilo, metilsulfonilo, etilsulfonilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-di-metilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil) etilo, 2-(N,N-di-metilcarbamoil)etilo, acetilmetilo, 2-acetiletilo, metoxycarbonilmetilo y 2-metoxycarboniletilo,

y en donde cualquier grupo heterociclilo en el grupo Q^1 -Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

R^3 es hidrógeno;

L es un enlace directo; y

Q^2 es un grupo arilo de fórmula Ib



Ib

en donde G^3 es un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, $N(R^{20})$, CO, $CH(OR^{20})$ y $C(R^{20})_2NR^{20}$, en donde R^{20} es hidrógeno o metilo, y Q^{10} es un grupo fenilo o bencilo, el cual se sustituye opcionalmente con 1 ó 2 sustituyentes seleccionados de fluoro, cloro, bromo, trifluorometilo, nitro, metilo, etilo, isopropilo, etinilo y ciano,

o Q^{10} es una fracción heteroarilo seleccionada de 2-1H-imidazolilo, 2-1H-imidazolilmetilo, 4-tiazolilmetilo, 2-tienilmetilo, 1,2,5-tiadiazol-3-ilo, 1,2,5-tiadiazol-3-ilmetilo, 3-isoxazolilmetilo, 2-, 3- ó 4-piridilo, 2-, 3- ó 4-piridilmetilo, 8-quinolinilo, y 8-quinolinilmetilo, la cual fracción heteroarilo se sustituye opcionalmente con uno o dos sustituyentes seleccionados de fluoro, cloro, bromo, trifluorometilo, metilo, etinilo y ciano;

y cada uno de G^2 y G^4 independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, metilo, y etinilo;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y se selecciona de metoxi y 3-(R)-dimetilaminopirrolidin-1-ilo,

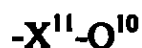
el grupo Q^1-Z se selecciona de piperidin-4-iloxi, 1-metilpiperidin-4-iloxi, 1-propilpiperidin-4-iloxi, 1-metilpiperidin-4-iloxi, 1-alilpiperidin-4-iloxi, 1-(2-propinilpiperidin-4-iloxi, 1-(-2-metoxietil)piperidin-4-iloxi, 1-acetilmetilpiperidin-4-iloxi, 1-tert-butoxicarbonilpiperidin-4-iloxi, 1-metoxycarbonilmetilpiperidin-4-iloxi, 1-metanosulfonilpiperidin-4-iloxi y 1-carbamoilmetilpiperidin-4-iloxi;

R^3 es hidrógeno;

L es un enlace directo; y

Q^2 es un grupo arilo de fórmula Ib como se define arriba en el texto en donde

G^3 se selecciona de un grupo de la fórmula:



en donde X^{11} se selecciona de O, S, NH, $N(CH_3)$, CO y CH_2NH , y Q^{10} se

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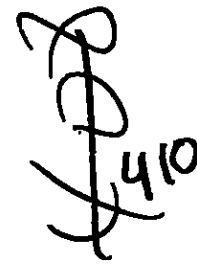
selecciona de fenilo o bencilo, 2-tienilo, 2-tienilmetilo, 2-1H-imidazolilo, 2-1H-imidazolilmetilo, 3-isoxazolilmetilo, 4-tiazolilo, 3-(1,2,5-tiadiazolil), 2-piridilo, 2-piridilmetilo, 3-piridilo, 3-piridilmetilo, 4-piridilo, 4-piridilmetilo y 8-quinolinilo, cual se sustituye opcionalmente por 1 ó 2 sustituyentes seleccionado de fluoro, cloro, metilo, nitro y ciano, y cada uno de G² y G⁴ independientemente se selecciona de hidrógeno y cloro; o una sal farmacéuticamente aceptable del mismo.

Valores apropiados para G³ en esta incorporación incluyen, por ejemplo fenoxi, 3-fluorofenoxi, 2,3-difluorofenoxi, feniltio, 2-fluorobenciloxi, 2-clorobenciloxi, 2-cianobenciloxi, 3-fluorobenciloxi, 3-fluorobenciloxi, 3-metilbenciloxi, 4-fluorobenciloxi, 2-metoxibenciloxi, 2,6-difluorobenciloxi, 2,6-diclorobenciloxi, 2, 5-dimetilbenciloxi, 4-metil-2-nitrobenciloxi, 3-fluorofenilaminometilo, 5-cloro-2-tienilo, 2-tienilcarbonilo, 1-metil-2-1H-imidazoliloxi, 1-metil-2-1H-imidazolilmetoxi, 5-metil-3-isoxazolilmetoxi, 2-metil-4-tiazolilmetoxi, 1,2,5-tiadiazol-3-ilmetoxi, 2-piridiloxi, 3-piridiloxi, 2-piridilmetoxi, 3-piridilmetoxi, 4-piridilmetoxi, 6-cloro-3-piridilmetoxi, N-(2-piridilmetil)amino, N-(2-piridil)-N-(metil)amino, N-(2-piridilmetil)-N-metilamino, 2-pirimidiniloxi y 8-quinoliniltio.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R¹, cuando está presente, se localiza en la posición 7 y se selecciona de metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-4-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R¹ se separan opcionalmente por la inserción



en la cadena de un grupo seleccionado de O, NH y N(CH₃),

y en donde cualquier grupo terminal CH₃ en una cadena (1-6C)alcoxi en un sustituyente R¹ lleva opcionalmente en el grupo terminal CH₃ un sustituyente seleccionado de hidroxilo, amino y N-(1-metilpirrolidin-3-il)-N-metilamino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R¹ lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en un sustituyente R¹ lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahydrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo;

el grupo Q¹-Z- se selecciona de ciclopentilo, tetrahydrofuran-3-ilo, tetrahidropiran-4-ilo, tetrahidrotiopiran-4-ilo, 1,1-dioxotetrahidrotiopiran-4-ilo, 1-oxotetrahidrotiopiran-4-ilo, tetrahidrotien-3-ilo, 1,1-dioxotetrahidrotien-3-ilo, 1-oxotetrahidrotien-3-ilo, pirrolidin-3-ilo, pirrolidin-2-ilo, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-3-ilo, homopiperidin-4-ilo y azetidin-3-ilo,

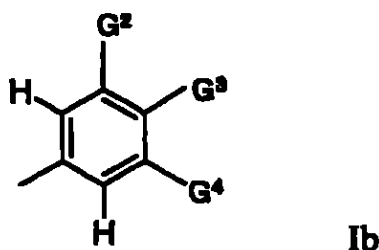
y en donde el grupo azetidinilo, pirrolidinilo, piperidinilo u homopiperidinilo en el grupo Q¹-Z- es opcionalmente N-sustituido por un sustituyente seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, tert-butilo, alilo, 2-propinilo, acetilo, propionilo, metoxycarbonilo, etoxycarbonilo, propoxycarbonilo, tert-butoxycarbonilo, metilsulfonilo, etilsulfonilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-di-metilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-di-metilcarbamoil)etilo, acetilmetilo, 2-acetiletilo, metoxycarbonilmetilo y 2-metoxycarboniletilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

R³ es hidrógeno;

L es un enlace directo o CH(CH₃); y

Q^2 es un grupo arilo de fórmula Ib



en donde G^3 se selecciona de hidrógeno, fluoro, cloro, bromo, hidroxilo, trifluorometilo, metilo, etilo, y etinilo, o de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO_2 , $N(R^{20})$, CO, $CH(OR^{20})$, $C(R^{20})_2O$, $C(R^{20})_2NR^{20}$, y $C(R^{20})_2S$, en donde R^{20} es hidrógeno, metilo o etilo, y Q^{10} es un grupo fenilo, bencilo o 2-feniletilo, el cual se sustituye opcionalmente con 1 ó 2 sustituyentes seleccionados de fluoro, cloro, bromo, trifluorometilo, nitro, metilo, etilo, isopropilo, vinilo, etinilo y ciano,

o Q^{10} es una fracción heteroarilo seleccionada de furilo, furilmetilo, 2-(fural)etilo, tienilo, tienilmetilo, 2-(tienil)etilo, oxazolilo, oxazolilmetilo, 2-(oxazolil)etilo, isoxazolilo, isoxazolilmetilo, 2-(isoxazolil)etilo, imidazolilo, imidazolilmetilo, 2-(imidazolil)etilo, tiazolilo, tiazolilmetilo, 2-(tiazolil)etilo, 1,2,4-triazolilo, 1,2,4-triazolilmetilo, 2-(1,2,4-triazolil)etilo, 1,2,5-tiadiazolilo, 1,2,5-tiadiazolilmetilo, 2-(1,2,5-tiadiazolil)etilo, piridilo, piridilmetilo, 2-(piridil)etilo, pirimidinilo, pirimidinilmetilo, 2-(pirimidinil)etilo, 1,3-benzodioxolilo, 1,3-benzodioxolilmetilo, 2-(1,3-benzodioxolil)etilo, quinolinilo, quinolinilmetilo, 2-(quinolinil)etilo, isoquinolinilo, isoquinolinilmetilo, 2-(isoquinolinil)etilo, quinazolinilo, quinazolinilmetilo y 2-(quinazolinil)etilo, el cual se sustituye opcionalmente con uno o dos sustituyentes seleccionado de fluoro, cloro, bromo, nitro, metilo, trifluorometilo, etilo, isopropilo, metoxi y etoxi;

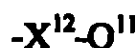
o cuando X^{11} es CO, Q^{10} puede ser también un nitrógeno de 5 a 10 miembros que contiene un grupo heterocíclico enlazado a X^{11} por un átomo de nitrógeno, llevando dicho grupo heterocíclico, que contiene nitrógeno,

en forma opcional 1 ó 2 sustituyentes seleccionados de fluoro, cloro, ciano, metilo, amino, metilamino y di-metilamino,

y cada uno de G^2 y G^4 independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, hidroxilo, trifluorometilo, metilo y etinilo,

o G^3 y G^4 juntos forman un grupo de fórmula: - -NH-CH=CH- , - CH=CH-NH- , - -NH-N=CH- , - -CH=N-NH- , - -S-N=CH- ó - -CH=N-S- ,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo de la fórmula:



en donde X^{12} es un enlace directo o se selecciona de SO_2 y CO, en donde Q^{11} es fenilo, bencilo, 2-feniletilo, 2-furilo, furfurilo, 3-furilo, 3-furilmetilo, 2-oxazolilo, 4-oxazolilo, 2-oxazolilmetilo, 4-oxazolilmetilo, 2-imidazolilo, 4-imidazolilo, 2-imidazolilmetilo, 4-imidazolilmetilo, 2-, 3- ó 4-piridilo, 2-, 3- ó 4-piridilmetilo, 2-(2-, 3- ó 4-piridil)etilo, 2-, 4- ó 5- pirimidinilo, 2-, 4- ó 5-pirimidinilmetilo, 2-(2-, 4- ó 5-pirimidinil)etilo, 1,2,4-triazol-3-ilo, 1,2,4-triazol-5-ilmetilo, triazol-3-ilmetilo, 1,2,4-triazol-5-il 2-tienilo, 3-tienilo, 2-tienilmetilo, 3-tienilmetilo, 2-(2-tienil)etilo, 2-(3-tienil)etilo, 2-tiazolilo, 4-tiazolilo, 2-tiazolilmetilo, 4-tiazolilmetilo, 1,2,5-tiadiazol-3-ilo, 1,2,5-tiadiazol-3-ilmetilo, 2-(1,2,5-tiadiazol-3-il)etilo, el cual lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, hidroxilo, metilo y etilo,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en un átomo de carbono disponible en la porción heteroarilo del anillo bicíclico 1 sustituyente seleccionado de fluoro, cloro, bromo, ciano, hidroxilo, amino, metilo, etilo, isopropilo, vinilo, etinilo, metilamino y di-metilamino;

a condición que cuando L es un enlace directo, por lo menos uno de G^2 , G^3 y G^4 es distinto de H; o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la

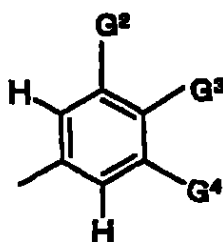
posición 7 y se selecciona de metoxi, 2-metoxietoxi, 3-(R)-dimetilaminopirrolidin-1-ilo, 1-metilpiperidin-4-ilmetoxi, 3-(N-(2-hidroxietil)-N-metilamino)propoxi, 2-(N-(2-metoxietil)N-metilamino)etoxi, 2-(N-(2-hidroxietil)-N-metilamino)etoxi, 3-(N-(2-dimetilaminoetil)-N-metilamino)propoxi, 2-(N-(2-dimetilaminoetil)-N-metilamino)etoxi, 3-pirrolidin-1-ilpropoxi, 3-(3-hidroxi-pirrolidin-1-il)propoxi, 2-pirrolidin-1-iletoxi, 2-(3-hidroxi-pirrolidin-1-il)etoxi, 2-(3-dimetilaminopirrolidin-1-il)etoxi, 3-(3-dimetilaminopirrolidin-1-il)propoxi, 3-(N-metil-N-(1-metilpirrolidin-3-il)amino)propoxi, 2-(N-metil-N-(1-metilpirrolidin-3-il)amino)etoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 3-(4-metilpiperazin-1-il)propoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-isopropilpiperazin-1-il)propoxi, 2-(4-isopropilpiperazin-1-il)etoxi, 3-(4-(2-metoxietil)piperazin-1-il)propoxi, 2-(4-(2-metoxietil)piperazin-1-il)etoxi, 2-(4-(2-morfolinoetil)piperazin-1-il)etoxi, 3-(4-(2-morfolinoetil)piperazin-1-il)propoxi, 2-(4-tetrahidrofurfuril)piperazin-1-iletoxi, 3-(4-tetrahidrofurfuril)piperazin-1-ilpropoxi, 2-(4-(1-metilpiperidin-4-il)piperazin-1-iletoxi, 3-(4-(1-metilpiperidin-4-il)piperazin-1-ilpropoxi, 2-(4-metilhomopiperazin-1-il)etoxi, 3-(4-metilhomopiperazin-1-il)propoxi, el grupo Q¹-Z- se selecciona de ciclopentiloxi, 1-metilazetidin-3-iloxi, 1-isopropilazetidin-3-iloxi, tetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, tetrahidrofuran-3-iloxi, 1-metilpirrolidin-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, piperidin-4-iloxi, 1-metilpiperidin-4-iloxi, 1-etilpiperidin-4-iloxi, 1-propilpiperidin-4-iloxi, 1-(2-metoxietil)piperidin-4-iloxi, 1-acetilpiperidin-4-iloxi, 1-acetilmetilpiperidin-4-iloxi, 1-alilpiperidin-4-iloxi, 1-(2-propinil)piperidin-4-iloxi, 1-metoxycarbonilmetilpiperidin-4-iloxi, 1-carbamoilmetilpiperidin-4-iloxi y 1-metanosulfonilpiperidin-4-iloxi;

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R^3 es hidrógeno;

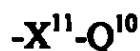
L es un enlace directo o $CH(CH_3)$; y

Q^2 es un grupo arilo de fórmula Ib



Ib

en donde G^3 se selecciona de hidrógeno, fluoro, cloro, bromo, metilo, y etinilo, o de un grupo de la fórmula:



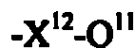
en donde X^{11} es un enlace directo o se selecciona de O, S, $N(R^{20})$, $C(R^{20})_2$, $N(R^{20})$ y CO, en donde R^{20} es hidrógeno o metilo, y Q^{10} se selecciona de fenilo o bencilo, 2-tienilo, 2-tienilmetilo, 2-1H-imidazolilo, 2-1H-imidazolilmetilo, 3-isoxazolilmetilo, 4-tiazolilo, 3-(1,2,5-tiadiazolilo), 2-piridilo, 2-piridilmetilo, 3-piridilo, 3-piridilmetilo, 4-piridilo, 4-piridilmetilo y 8-quinolinilo, cual se sustituye opcionalmente por 1 ó 2 sustituyentes seleccionados de fluoro, cloro, metilo, isopropilo, trifluorometilo, nitro y ciano,

o cuando X^{11} es CO, Q^{10} puede seleccionarse también de pirrolidin-1-ilo, piperidino, homopiperidino, morfolino, piperazin-1-ilo, homopiperazin-1-ilo, decahidroquinolin-1-ilo y decahidroquinolin-1-ilo,

y cada uno de G^2 y G^4 independientemente se selecciona de hidrógeno, fluoro, cloro, bromo, trifluorometilo, metilo y etinilo,

o G^3 y G^4 juntos forman un grupo de fórmula: -NH-CH=CH-, -NH-N=CH- ó -S-N=CH-,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo de la fórmula:



en donde X^{12} es un enlace directo o es SO_2 , y Q^{11} es fenilo, bencilo, ó 2-

piridilmetilo, el cual lleva opcionalmente un sustituyente fluoro,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la posición 3 un sustituyente cloro; a condición que cuando L es un enlace directo, por lo menos uno de G^2 , G^3 y G^4 es distinto de H; o una sal farmacéuticamente aceptable del mismo.

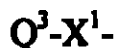
Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y se selecciona de metoxi, 2-metoxietoxi y 3-(R)-dimetilaminopirrolidin-1-ilo; el grupo Q^1-Z se selecciona de piperidin-4-iloxi, 1-metilpiperidin-4-iloxi y tetrahidropiran-4-iloxi;

el grupo Q^2LNR^3 se selecciona de 3-cloroanilino, 3-bromoanilino, 3-cinoanilino, 3-metilanilino, 3-cloro-4-fluoroanilino, indol-5-ilamino, 3-cloroindol-5-ilamino, 1-(3-fluorobencil)indazol-5-ilamino, 3-cloro-4-fenoxianilino, 3-cloro-4-(3-fluorobenciloxi)anilino, 3-cloro-4-((decahidroquinolin-1-il)carbonil)anilino, 3-cloro-4-((decahidroisoquinolin-2-il)carbonil)anilino, 3-cloro-4-((3-metilpiperidin-1-il)carbonil)anilino y 3-etinil-4-((decahidroquinolin-1-il)carbonil)anilino; o una sal de adición de ácido, farmacéuticamente aceptable, del mismo.

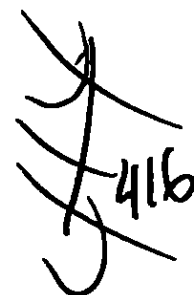
Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y se selecciona de (1-6C)alcoxi, (2-6C)alqueniloxi y (2-6C)alquiniloxi, o de un grupo de la fórmula:

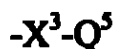


en donde X^1 es un enlace directo o es O, y Q^3 es heterociclilo o heterociclil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, y $N(R^5)$, en donde R^5 es hidrógeno o (1-6C)alquilo,



y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, amino, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, o de un grupo de la fórmula:

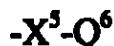


en donde X^3 es un enlace directo o es $\text{N}(\text{R}^7)$, en donde R^7 es hidrógeno o (1-6C)alquilo, y Q^5 es heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, o de un grupo de la fórmula:



en donde X^4 es un enlace directo y R^8 es hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N -(1-6C)alquilcarbamoilo-(1-6C)alquilo, N,N -di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^5 es un enlace directo y Q^6 es heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de hidroxilo, amino, (1-6C)alquilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino, y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 sustituyente oxo;

Z es O;

Q^1 se selecciona de azetidin-3-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, tetrahydrofuran-3-ilo, tetrahydropiran-3-ilo y tetrahydropiran-4-ilo (convenientemente tetrahydrofuran-3-ilo, tetrahydropiran-4-ilo o más convenientemente piperidin-4-ilo), y en donde cualquier grupo NH en un grupo heterociclilo en Q^1 lleva opcionalmente un sustituyente seleccionado de metilo, etilo, alilo, 2-metoxietilo,

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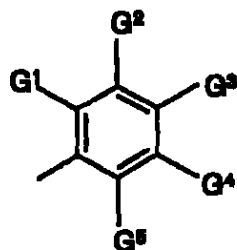
carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo y metoxicarbonilmetilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 sustituyente oxo;

R² y R³ son hidrógeno;

L es un enlace directo;

Q² es un grupo arilo de fórmula Ia



Ia

en donde G¹, G² y G⁵ son hidrógeno,

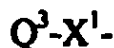
G⁴ se selecciona de hidrógeno, halógeno, (1-6C)alquilo, (2-8C)alquenilo y (2-8C)alquinilo y

G³ se selecciona de hidrógeno, halógeno e hidroxilo, con la condición que G³ y G⁴ no son ambos hidrógeno, o G³ y G⁴ juntos forman un grupo de fórmula: -NH-CH=CH- ó -NH-N=CH-,

y el anillo heteroarilo bicíclico de 9 miembros, formado cuando G³ y G⁴ juntos se enlazan, lleva opcionalmente en la porción heteroarilo del anillo bicíclico 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, ciano y (1-6C)alquilo; o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R¹, cuando está presente se localiza en la posición 7 y se selecciona de (1-3C)alcoxi, (1-3C)alcoxi(1-3C)alcoxi y un grupo de la fórmula :



en donde X¹ es O y Q³ es 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo,

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piperidin-4-ilmetilo, 2-homopiperidin-1-iletilo, 3-homopiperidin-1-ilpropilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo, 2-homopiperazin-1-iletíl o 3-homopiperazin-1-ilpropilo,

y en donde cualquier grupo heterociclilo en un sustituyente R^1 lleva opcionalmente un sustituyente seleccionado de hidroxí, carbamoilo, metilo, etilo, alilo, 2-propinilo, acetilo, N-metilcarbamoíl N,N-dimetilcarbamoíl, 2-metoxietilo, carbamoílmetilo, N,N-dimetilcarbamoílmetilo, acetilmetilo y cianometilo,

y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 sustituyente oxo, o

R^1 es 3-(R)-dimetilaminopirrolidin-1-ilo;

Z es O;

Q^1 se selecciona de azetidin-3-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, tetrahidrofuran-3-ilo, tetrahidropiran-3-ilo y tetrahidropiran-4-ilo (convenientemente piperidin-4-ilo o tetrahidrofuran-3-ilo), y

en donde cualquier grupo NH en un grupo heterociclilo en Q^1 lleva opcionalmente un sustituyente seleccionado de metilo, 2-metoxietilo, carbamoílmetilo, N-metilcarbamoílmetilo, N,N-dimetilcarbamoílmetilo y metoxicarbonilmetilo,

y en donde cualquier grupo heterociclilo en el grupo Q^1 -Z- lleva opcionalmente 1 sustituyente oxo;

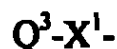
R^2 es hidrógeno; y

$Q^2LN(R^3)$ se selecciona de 3-cloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-cloroanilino, 3-metilanilino y 3-etilanilino;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de metoxi, 2-metoxietoxi y un grupo de la fórmula:



en donde X^1 es O y Q^3 es 3-pirrolidin-1-ilpropoxi, 3-morfolinopropoxi, 3-

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piperidinopropoxi, y 3-piperazin-1-ilpropoxi,

y en donde cualquier grupo heterociclilo en un sustituyente R^1 lleva opcionalmente un sustituyente seleccionado de hidroxilo, carbamoilo, metilo, etilo, alilo, acetilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, 2-metoxietilo, carbamoilmetilo y N,N-dimetilcarbamoilmetilo,

y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 sustituyente oxo;

Z es O;

Q^1 se selecciona de piperidin-3-ilo, piperidin-4-ilo, tetrahidrofuran-3-ilo, tetrahidropiran-3-ilo y tetrahidropiran-4-il (convenientemente piperidin-4-ilo o terahidrofuran-3-ilo), y

en donde cualquier grupo NH en un grupo heterociclilo en Q^1 lleva opcionalmente un sustituyente seleccionado de metilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo y metoxicarbonilmetilo,

y en donde cualquier grupo heterociclilo en el grupo Q^1 -Z- lleva opcionalmente 1 sustituyente oxo;

R^2 es hidrógeno; y

$Q^2LN(R^3)$ se selecciona de 3-cloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-cloroanilino, 3-metilanilino y 3-etinilanilino; o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

R^2 es hidrógeno;

$Q^2LN(R^3)$ se selecciona de 3-cloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-cloroanilino, 3-metilanilino y 3-etinilanilino (convenientemente 3-cloro-4-fluoroanilino ó 3-etinilanilino); y

(i) m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de metoxi y 2-metoxietoxi;

Z es O;

Q^1 se selecciona de piperidin-4-ilo y piperidin-3-ilo (convenientemente

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piperidin-4-ilo), y

en donde cualquier grupo NH en un grupo piperidinilo en Q¹ lleva opcionalmente un sustituyente seleccionado de metilo, carbamoilmetilo y N,N-dimetilcarbamoilmetilo, o

(ii) m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de 3-pirrolidin-1-ilpropoxi, 3-morfolinopropoxi y 3-piperazin-1-ilpropoxi,

y en donde cualquier grupo NH en un piperazinilo en R¹ lleva opcionalmente un sustituyente seleccionado de metilo, carbamoilmetilo y N,N-dimetilcarbamoilmetilo,

y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 sustituyente oxo;

Z es O; y

Q¹ se selecciona de tetrahidropiran-3-ilo, tetrahidropiran-4-ilo y tetrahidrofuran-3-ilo (convenientemente tetrahidrofuran-3-ilo),

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 sustituyente oxo;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de 5-pirrolidin-1-ilpropoxi, 3-pirrolidin-2-ilpropoxi, 3-pirrolidin-3-ilpropoxi, 5-morfolinopropoxi, 3-piperidinopropoxi, 3-piperidin-2-ilpropoxi, 3-piperidin-3-ilpropoxi, 3-piperidin-4-ilpropoxi y 3-piperazin-1-ilpropoxi,

y en donde cualquier grupo heterociclilo en un sustituyente R¹ lleva opcionalmente un sustituyente seleccionado de hidroxilo, carbamoilo, metilo, etilo, alilo, acetilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, 2-metoxietilo, carbamoilmetilo, N,N-dimetilcarbamoilmetilo, acetilmetilo y cianometilo,

y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 sustituyente oxo;

Z es O;

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Q^1 es tetrahidrofuran-3-ilo, tetrahidropiran-4-il o tetrahidropiran-3-ilo,

R^2 es hidrógeno; y

$Q^2LN(R^3)$ se selecciona de 3-cloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-cloroanilino, 3-metilanilino y 3-etilanilino;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente se localiza en la posición 7 y se selecciona de (1-3C)alcoxi y (1-3C)alcoxi(1-3C)alcoxi (por ejemplo metoxi ó 2-metoxietoxi);

Z es O;

Q^1 se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo (convenientemente piperidin-4-ilo), y

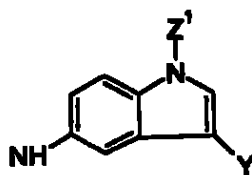
en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q^1 lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, o de un grupo de la fórmula:



en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-dimetilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo, y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q^1 -Z- lleva opcionalmente 1 sustituyente oxo;

R^2 es hidrógeno; y

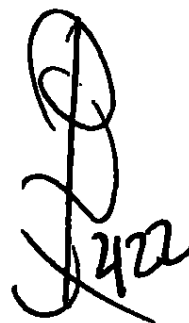
$Q^2LN(R^3)$ es un grupo de la fórmula Ic:



Ic

en donde Z^1 es hidrógeno o (1-4C)alquilo (convenientemente hidrógeno), y

Y se selecciona de hidrógeno, halógeno, (1-4C)alquilo y ciano



(convenientemente hidrógeno, cloro o bromo, más convenientemente cloro o bromo);

o una sal farmacéuticamente aceptable del mismo.

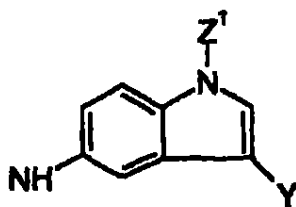
Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente se localiza en la posición 7 y es metoxi;

Z es O;

Q^1 es 1-metilpiperidin-4-ilo; R^2 es hidrógeno; y

$Q^2LN(R^3)$ es un grupo de la fórmula Ic:



Ic

en donde Z^1 es hidrógeno, y

Y se selecciona de hidrógeno, cloro y bromo;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-3C)alcoxi y (1-3C)alcoxi(1-3C)alcoxi (por ejemplo metoxi ó 2-metoxietoxi);

Z es O;

Q^1 se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo (convenientemente piperidin-4-ilo), y

en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q^1 lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo y N,N-dimetilcarbamoilo, o de un grupo de la fórmula:



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en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-dimetilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo,

y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q^1 -Z lleva opcionalmente 1 sustituyente oxo;

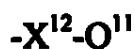
R^2 y R^3 son hidrógeno;

L es un enlace directo; y

Q^2 es un grupo de fórmula Ia como se define arriba en el texto en donde:

G^1 , G^2 y G^5 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-NH-CH=CH-$, y el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono, a los cuales se unen, se sustituye en la posición 1 por un grupo de la fórmula:



en donde X^{12} es un enlace directo y Q^{11} es bencilo el cual se sustituye opcionalmente por 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, metilo y etilo, (por ejemplo Q^{11} es 2-fluorobencilo o 3-fluorobencilo), y

y en donde el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye opcionalmente en la posición 3 por un sustituyente seleccionado de cloro y bromo;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y es metoxi;

Z es O;

Q^1 es 1-metilpiperidin-4-ilo;

R^2 y R^3 son hidrógeno;

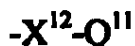
L es un enlace directo; y

Q^2 es un grupo de fórmula Ia como se define arriba en el texto en donde:

G^1 , G^2 y G^5 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-NH-CH=CH-$, y el

anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye en la posición 1 por un grupo de la fórmula:



en donde X^{12} es un enlace directo y Q^{11} es bencilo el cual se sustituye opcionalmente por 1 sustituyente fluoro, (por ejemplo Q^{11} es 2-fluorobencilo o 3-fluorobencilo);

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-3C)alcoxi, (1-3C)alcoxi(1-3C)alcoxi y piperidin-4-ilmetoxi (por ejemplo R^1 es metoxi ó 2-metoxietoxi);

Z es O;

Q^1 se selecciona de pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo y tetrahidropiran-4-ilo (convenientemente piperidin-4-ilo), y

en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q^1 lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, o de un grupo de la fórmula:



en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-di-metilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo, y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q^1 -Z- lleva opcionalmente 1 sustituyente oxo;

R^2 y R^3 son hidrógeno;

L es un enlace directo; y

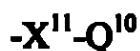
Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno,

G^4 se selecciona de cloro, metilo y etinilo, y

G^3 es un grupo de la fórmula:

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en donde X^{11} es O y Q^{10} es bencilo el cual se sustituye opcionalmente por 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, ciano y metilo;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y es metoxi;

Z es O;

Q^1 es 1-metilpiperidin-4-ilo;

R^2 y R^3 son hidrógeno;

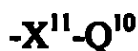
L es un enlace directo; y

Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^3 son hidrógeno,

G^4 es cloro, y

G^5 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} es bencilo el cual se sustituye opcionalmente por 1 sustituyente fluoro (por ejemplo $-X^{11}-Q^{10}$ es 3-fluorobenciloxi o benciloxi); o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-3C)alcoxi y (1-3C)alcoxi(1-3C)alcoxi (por ejemplo metoxi ó 2-metoxietoxi);

Z es O;

Q^1 se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo (convenientemente piperidin-4-ilo), y

en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q^1 lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxicarbonilo, etoxicarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, o de un grupo de la fórmula:

2
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en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-di-metilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo, y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q^1 -Z- lleva opcionalmente 1 sustituyente oxo;

R^2 y R^3 son hidrógeno;

L es un enlace directo; y

Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno,

G^4 se selecciona de cloro y metilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} se selecciona de isoxazolilmetilo y tiazolilmetilo (por ejemplo 3-isoxazolilmetilo o 4-tiazolilmetilo), y en donde el grupo heteroarilo en Q^{10} lleva opcionalmente un sustituyente metilo;

o una sal farmacéuticamente aceptable del mismo.

Una incorporación adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y es metoxi;

Z es O;

Q^1 es 1-metilpiperidin-4-ilo;

R^2 y R^3 son hidrógeno;

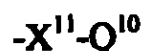
L es un enlace directo; y

Q^2 es un grupo de fórmula Ia en donde:

G^1 , G^2 y G^5 son hidrógeno,

G^4 se selecciona de cloro y metilo (convenientemente metilo), y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} se selecciona de 3-isoxazolilmetilo y 4-tiazolilmetilo, y en donde el grupo heteroarilo en Q^{10} lleva opcionalmente 1

sustituyente metilo (por ejemplo Q¹⁰ es 5-metil-isoxazol-3-ilmetilo, ó 4-tiazolilmetilo);

o una sal farmacéuticamente aceptable del mismo.

Un compuesto preferido particular, adicional, de la invención es, por ejemplo, un derivado de quinazolina de la Fórmula I seleccionado de:

4-(3-cloroanilino)-7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina;
4-(3-cloroindol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina;
4-(3-bromoanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloroindol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina;
4-(3-etinilanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina;
4-(3-cloroanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 7-metoxi-4-(3-metilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-bromoanilino)-7-(2-metoxietoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina;
4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-(piperidin-1-il)propoxi)quinazolina;
4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-(4-isopropilpiperazin-1-il)etoxi)quinazolina;
4-(3-cloro-4-fluoroanilino)-7-[3-(*N*-(2-hidroxietyl)-*N*-metilamino) propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina;
4-(3-cloro-4-fluoroanilino)-7-[3-(*N*-(2-dimetilaminoetyl)-*N*-metilamino) propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina; y
4-(3-cloro-4-fluoroanilino)-7-(3-(4-metilpiperazin-1-il)propoxi)-5-(tetrahidrofuran-3-iloxi)quinazolina;

o una sal de adición de ácido farmacéuticamente aceptable del mismo;

Un compuesto preferido particular, adicional, de la invención es, por ejemplo, un derivado de quinazolina de la Fórmula I seleccionado de:

4-(3-bromoanilino)-7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina;



4-(3-bromoindol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)
quinazolina;

4-(3-cloro-4-benciloxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)
quinazolina;

4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-
iloxi)quinazolina;

4-(3-metil-4-(5-metilisoxazol-3-ilmetoxi)anilino)-7-metoxi-5-(1-
metilpiperidin-4-iloxi)quinazolina;

4-(3-metil-4-(tiazol-4-ilmetoxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-
iloxi)quinazolina;

4-(1-(3-fluorobencil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-
iloxi)quinazolina; y

4-(1-(2-fluorobencil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-
iloxi)quinazolina;

o una sal de adición de ácido farmacéuticamente aceptable del mismo.

Un compuesto preferido particular, adicional, de la invención es, por
ejemplo, un derivado de quinazolina de la Fórmula I seleccionado de:

4-(3-cloro-4-fluoroanilino)-7-(3-morfolinopropoxi)-5-(tetrahidrofuran-3-
iloxi)quinazolina;

4-(3-cloro-4-fluoroanilino)-7-(3-pirrolidin-1-ilpropoxi)-5-(tetrahidrofuran-
3-iloxi)quinazolina;

2-[4-(4-(3-cloro-4-fluoroanilino)-7-metoxiquinazolin-5-iloxi) piperidin-1-
il]acetamida;

4-(3-cloro-4-fluoroanilino)-7-(2-metoxietoxi)-5-(1-metilpiperidin-4-iloxi)
quinazolina; y

4-(3-cloro-4-fluoroanilino)-7-[3-(4-(N,N-dimetilcarbamoilmetil) piperazin-
1-il)propoxi]-5-(tetrahidrofuran-3-iloxi)quinazolina;

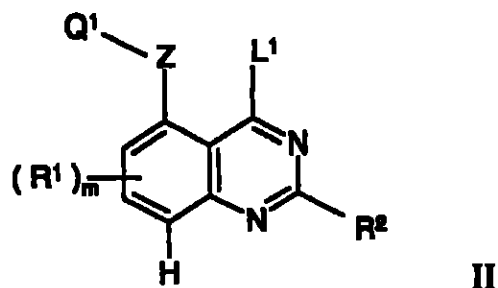
o una sal de adición de ácido, farmacéuticamente aceptable, del mismo.

Un derivado de quinazolina de la Fórmula I, o una sal
farmacéuticamente aceptable del mismo, puede prepararse por cualquier
proceso conocido por ser aplicable a la preparación de compuestos
químicamente relacionados. Tales procesos, cuando se emplean para

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preparar un derivado de quinazolina de la Fórmula I se proveen como una característica adicional de la invención y se ilustran por las siguientes variantes del proceso, representativas, en las cuales, a menos que se indique otra cosa, Q^1 , Z, m, R^1 , R^2 , R^3 , L y Q^2 tienen cualquiera de los significados definidos más arriba en el texto. Los materiales iniciales necesarios pueden obtenerse por procedimientos estándar de química orgánica. La preparación de tales materiales iniciales se describe en conjunción con las siguientes variantes representativas del proceso y en los Ejemplos que acompañantes. Alternativamente, los materiales iniciales necesarios son obtenibles por procedimientos análogos a los ilustrados los cuales forman parte de las habilidades ordinarias de un químico orgánico.

Proceso (a) La reacción, convenientemente en la presencia de una base apropiada, de una quinazolina de la Fórmula II



en donde L^1 es un grupo desplazable y Q^1 , Z, m, R^1 y R^2 tienen cualquiera de los significados definidos más arriba en el texto excepto que cualquier grupo funcional se protege, si es necesario, con un compuesto de la Fórmula



en donde Q^2 , L y R^3 tienen cualquiera de los significados definidos más arriba en el texto excepto que cualquier grupo funcional se protege, si es necesario, a partir de lo cual cualquier grupo protector que esté presente se retira por medios tradicionales.

Una base apropiada es, por ejemplo, una base amina orgánica tal como, por ejemplo, piridina, 2,6-lutidina, collidina, 4-dimetilaminopiridina, trietilamina, di-isopropiletilamina, N-metilmorfolina o diazabicyclo[5.4.0]undec-7-eno, o, por ejemplo, un carbonato de metal

alcalino o alcalinotérreo, por ejemplo carbonato de sodio, carbonato de potasio, carbonato de calcio o, por ejemplo, un hidruro de metal alcalino, por ejemplo hidruro de sodio.

Un grupo desplazable apropiado L^1 es, por ejemplo, un grupo halógeno, alcoxi, ariloxi, mercapto, alquiltio, ariltio, alquilsulfinilo, arilsulfinilo, alquilsulfonilo, arilsulfonilo o sulfonilo, por ejemplo un grupo cloro, bromo, metoxi, fenoxi, pentafluorofenoxi, metiltio, metanosulfinilo, metanosulfonilo o tolueno-4-sulfonilo. La reacción se lleva convenientemente a cabo en la presencia de un solvente o diluyente inerte apropiado, por ejemplo un alcohol o éster tal como metanol, etanol, isopropanol o acetato de etilo, un solvente halogenado tal como cloruro de metileno, cloroformo o tetracloruro de carbono, un éter tal como tetrahidrofurano o 1,4-dioxano, un solvente aromático tal como tolueno, o un solvente aprótico dipolar tal como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidin-2-ona o dimetilsulfóxido. La reacción se lleva convenientemente a cabo a una temperatura en el rango, por ejemplo, 10 a 250°C, preferiblemente en el rango 40 a 80°C.

La quinazolina de la Fórmula II puede hacerse reaccionar además con un compuesto de la Fórmula Q^2LNHR^3 en la presencia de un solvente prótico tal como isopropanol, convenientemente en la presencia de un ácido, por ejemplo gas de cloruro de hidrógeno en éter dietílico o dioxano, o ácido clorhídrico. Alternativamente, esta reacción puede llevarse convenientemente a cabo en un solvente aprótico, tal como dioxano o un solvente aprótico dipolar tal como N,N-dimetilacetamida en la presencia de un ácido, por ejemplo gas de cloruro de hidrógeno en éter dietílico o dioxano, o ácido clorhídrico. Las anteriores reacciones se llevan convenientemente a cabo a una temperatura en el rango, por ejemplo, 0 a 150°C, preferiblemente a temperatura de reflujo, o cerca de ella, del solvente de reacción.

El derivado de quinazolina de la Fórmula II, en donde L^1 es halógeno, puede hacerse reaccionar con un compuesto de la Fórmula Q^2LNHR^3 en la ausencia de un ácido o una base. En esta reacción, el desplazamiento del



grupo saliente halógeno L^1 se traduce en la formación del ácido HL^1 in-situ y la auto-catálisis de la reacción. Convenientemente la reacción se lleva a cabo en un solvente orgánico inerte apropiado, por ejemplo iso propanol, dioxano o N,N-dimetilacetamida. Las condiciones adecuadas para esta reacción son como se describe arriba.

El derivado de quinazolina de la Fórmula I puede obtenerse de este proceso en la forma de la base libre o, alternativamente, puede obtenerse en la forma de una sal con el ácido de la Fórmula $H-L^1$ en donde L^1 tiene el significado definido más arriba en el texto. Cuando se desea obtener la base libre a partir de la sal, la sal puede tratarse con una base apropiada, por ejemplo, un carbonato o hidróxido de metal alcalino o alcalinotérreo, por ejemplo carbonato de sodio, carbonato de potasio, carbonato de calcio, hidróxido de sodio o hidróxido de potasio.

Los grupos protectores pueden escogerse en general de cualquiera de los grupos descritos en la literatura o conocidos por el químico experto como apropiados para la protección del grupo en cuestión y pueden introducirse por métodos tradicionales. Los grupos protectores pueden retirarse por cualquier método conveniente como se describe en la literatura o conocido por el químico experto como apropiado para el retiro del grupo protector en cuestión, eligiéndose tales métodos de manera que efectúen el retiro del grupo protector con alteración mínima de grupos en algún otro punto en la molécula.

A continuación se incluyen efectos específicos de grupos protectores con fines de conveniencia, en los cuales "inferior", como en, por ejemplo, alquilo inferior, significa que el grupo al cual se aplica tiene preferiblemente 1-4 átomos de carbono. Se entenderá que estos ejemplos no son exhaustivos. Donde, a continuación, se dan ejemplos específicos de métodos para el retiro de grupos protectores, éstos similarmente no son exhaustivos. El uso de grupos protectores y métodos de desprotección no específicamente mencionados están, sin duda, en el ámbito de la invención.

Un grupo protector carboxi puede ser el residuo de un alcohol alifático o arilalifático que forma un éster, o de un silanol que forma un

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éster (conteniendo el dicho alcohol o silanol preferiblemente 1-20 átomos de carbono). Ejemplos grupos protectores carboxi incluyen grupos (1-12C)alquilo de cadena recta o ramificada (por ejemplo isopropilo, y tert-butilo); grupos alquilo inferior-alcoxi inferior (por ejemplo metoximetilo, etoximetilo e isobutoximetilo); grupos alquilo inferior-aciloxi inferior, (por ejemplo acetoximetilo, propioniloximetilo, butiriloximetilo y pivaloiloximetilo); grupos alquilo inferior-alcoxycarboniloxi inferior (por ejemplo 1-metoxycarboniloxietilo y 1-etoxycarboniloxietilo); grupos aril-alquilo inferior (por ejemplo bencilo, 4-metoxibencilo, 2-nitrobencilo, 4-nitrobencilo, benzhidrilo y ftalidilo); grupos tri(alquilo inferior)sililo (por ejemplo trimetilsililo y tert-butildimetilsililo); grupos alquilo inferior-tri(alquilo inferior)sililo (por ejemplo trimetilsililetilo); y grupos (2-6C)alquenilo (por ejemplo alilo). Métodos particularmente apropiados para el retiro de grupos protectores carboxilo incluyen por ejemplo escisión catalizada por un ácido, base, metal o enzima.

Ejemplos de grupos protectores hidroxí incluyen grupos alquilo inferior (por ejemplo tert-butilo), grupo alquenilo inferior (por ejemplo alilo); grupos alcanilo inferior (por ejemplo acetilo); grupos alcoxycarbonilo inferior (por ejemplo tert-butoxycarbonilo); grupos alqueniloxycarbonilo (por ejemplo aliloxycarbonilo); grupos alcoxycarbonilo-arilo inferior (por ejemplo benciloxycarbonilo, 4-metoxibenciloxycarbonilo, 2-nitrobenciloxycarbonilo y 4-nitrobenciloxycarbonilo); sililo tri(alquilo inferior) por ejemplo trimetilsililo y tert-butildimetilsililo) y grupos alquilo inferior-arilo (por ejemplo bencilo).

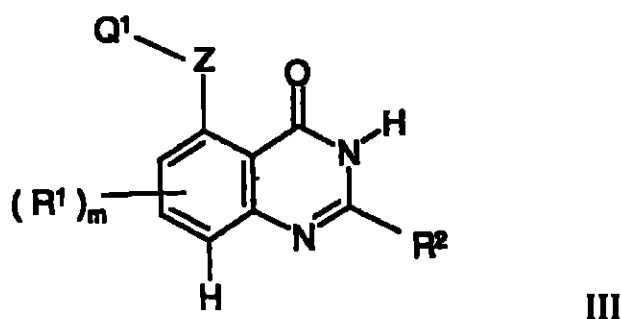
Ejemplos de grupos protectores amino incluyen grupos formilo, grupos alquilo inferior-arilo (por ejemplo bencilo y bencilo sustituido, 4-metoxibencilo, 2-nitrobencilo y 2,4-dimetoxibencilo, y grupos trifenilmetilo); di-4-anisilmetilo y furilmetilo; grupos alcoxycarbonilo inferior (por ejemplo tert-butoxycarbonilo); alqueniloxycarbonilo inferior (por ejemplo aliloxycarbonilo); alcoxycarbonilo inferior-arilo (por ejemplo benciloxycarbonilo, 4-metoxibenciloxycarbonilo, 2-nitrobenciloxycarbonilo y 4-nitrobenciloxycarbonilo); grupos alcaniloxialquilo inferior (por

ejemplo pivaloiloximetilo); grupos trialquilsililo (por ejemplo trimetilsililo y tert-butildimetilsililo); alquilideno (por ejemplo metilideno) y bencilideno y bencilideno sustituido.

Métodos apropiados para el retiro de grupos protectores hidroxí y amino incluyen, por ejemplo, hidrólisis catalizada por un ácido, base, metal o enzima para grupos tales como 2-nitrobenciloxicarbonilo, hidrogenación para grupos tales como bencilo y, fotolíticamente, para grupos tales como 2-nitrobenciloxicarbonilo. Por ejemplo un grupo protector tert-butoxicarbonilo puede retirarse de un grupo amino por una hidrólisis catalizada por ácido usando ácido trifluoroacético.

Se remite al lector a Advanced Organic Chemistry, 4th Edition, por J. March, publicada por John Wiley & Sons 1992, para guía general de condiciones de reacción y reactivos y a Protective Groups in Organic Synthesis, 2nd Edition, por T. Green *et al.*, también publicado por John Wiley & Son, para guía general con respecto a grupos protectores.

Materiales iniciales de quinazolina de la Fórmula II pueden obtenerse por procedimientos tradicionales. Por ejemplo, una 3,4-dihidroquinazolin-4-ona de fórmula III



en donde m, R¹, Q¹, Z y R² tienen cualquiera de los significados definidos más arriba en el texto excepto que cualquier grupo funcional se protege, si es necesario, puede hacerse reaccionar con un agente halogenante tal como cloruro de tionilo, cloruro de fosforilo o una mezcla de tetracloruro de carbono y trifenilfosfina, a partir de lo cual cualquier grupo protector, que esté presente, se retira por medios tradicionales. La reacción se lleva convenientemente a cabo en un solvente inerte apropiado,

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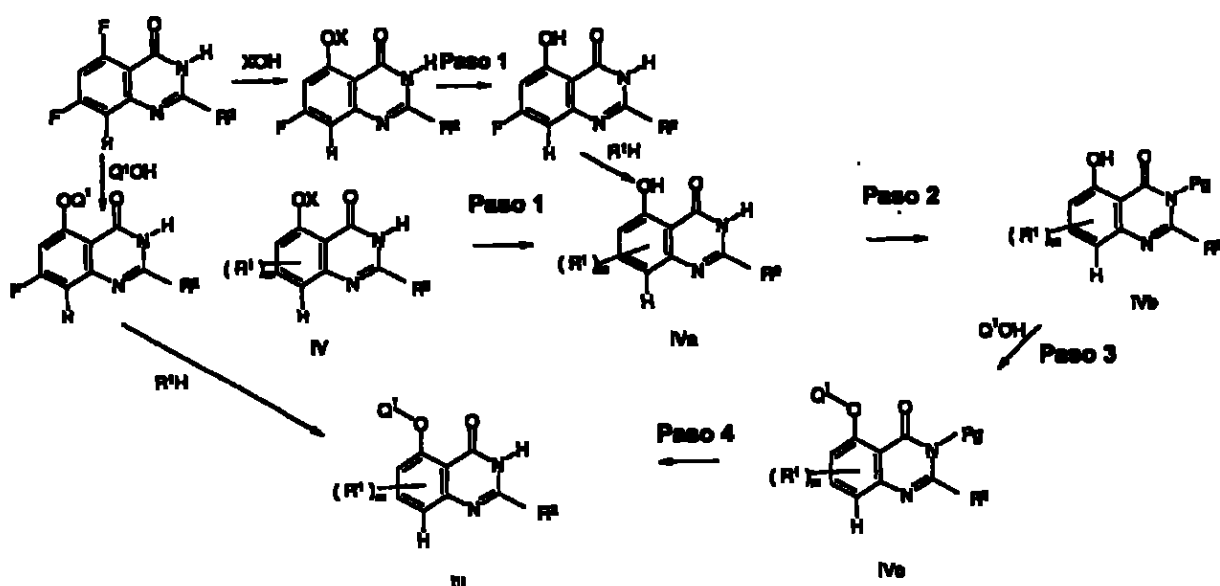
por ejemplo 1,2-dicloroetano o N,N-dimetilformamida convenientemente en la presencia de una base tal como una base orgánica, por ejemplo diisopropiletilamina. La reacción se lleva convenientemente a cabo a una temperatura en el rango, por ejemplo, 0 a 150°C, preferiblemente a temperatura de reflujo, o cerca de ella, del solvente de reacción.

La 4-cloroquinazolina así obtenida puede convertirse, si se requiere, en una 4-pentafluorofenoxiquinazolina por reacción con pentafluorofenol en la presencia de una base apropiada tal como carbonato de potasio y en la presencia de un solvente apropiado tal como N,N-dimetilformamida.

El compuesto de fórmula I puede prepararse también usando un proceso abreviado comenzando a partir del compuesto de fórmula III, en donde el compuesto de la Fórmula Q^2LNHR^3 se hace reaccionar con el compuesto de fórmula II luego de la halogenación del compuesto de fórmula III. El uso de tal proceso abreviado evita la necesidad de aislar el compuesto de fórmula II antes de la reacción con el compuesto de fórmula Q^2LNHR^3 .

La 3,4-dihidroquinazolin-4-ona de fórmula III puede obtenerse usando procedimientos tradicionales. Por ejemplo, cuando Z es un átomo de oxígeno, el compuesto de fórmula III puede prepararse como se ilustra por Esquema de Reacción 1 comenzando con el compuesto de fórmula IV.

Esquema de Reacción 1





en donde R^1 , R^2 y Q^1 son como se define arriba en el texto, X es un grupo protector hidroxilo apropiado tal como (1-6C)alquilo (por ejemplo metilo) o bencilo, y Pg es un grupo protector amina apropiado.

Notas:

Paso (1)

Cuando X es (1-6C)alquilo, puede escindirse del compuesto de fórmula IV por métodos tradicionales, tales como por tratamiento del compuesto de fórmula IV con, por ejemplo:

- (i) un (1-6C)alquilsulfuro de metal alcalino tal como etanotiolato de sodio;
- (ii) un diarilfosfuro de metal alcalino tal como difenilfosfuro de litio;
- (iii) un trihalogenuro de boro o aluminio tal como tribromuro de boro;
- (iv) bromuro de magnesio, preferiblemente en la presencia de una base apropiada, tal como una base orgánica, por ejemplo piridina; o
- (v) hidrocloreuro de piridina en piridina.

Generalmente, la reacción de escisión se lleva a cabo a una temperatura en el rango de desde, por ejemplo, 40 a 150°C.

Cuando X es bencilo, puede escindirse a partir del compuesto de fórmula IV por, por ejemplo, hidrólisis catalizada por ácido, por ejemplo por tratamiento del compuesto de fórmula IV con ácido trifluoroacético. Convenientemente la reacción se lleva a cabo a una temperatura en el rango de 30 a 120°C, por ejemplo 70°C.

Paso (2)

El grupo protector Pg se agrega a la 3,4-dihidro-5-hidroxiquinazolin-4-ona de fórmula IVa usando técnicas tradicionales. Por ejemplo un Pg apropiado es un grupo pivaloiloximetilo que puede agregarse al compuesto de fórmula IVa haciendo reaccionar el compuesto de fórmula IVa con clorometilpivalato en la presencia de una base apropiada tal como hidruro de sodio.

Paso (3)

El grupo Q^1O puede introducirse acoplando el compuesto de fórmula IVb con un alcohol de la Fórmula Q^1OH en la presencia de un agente

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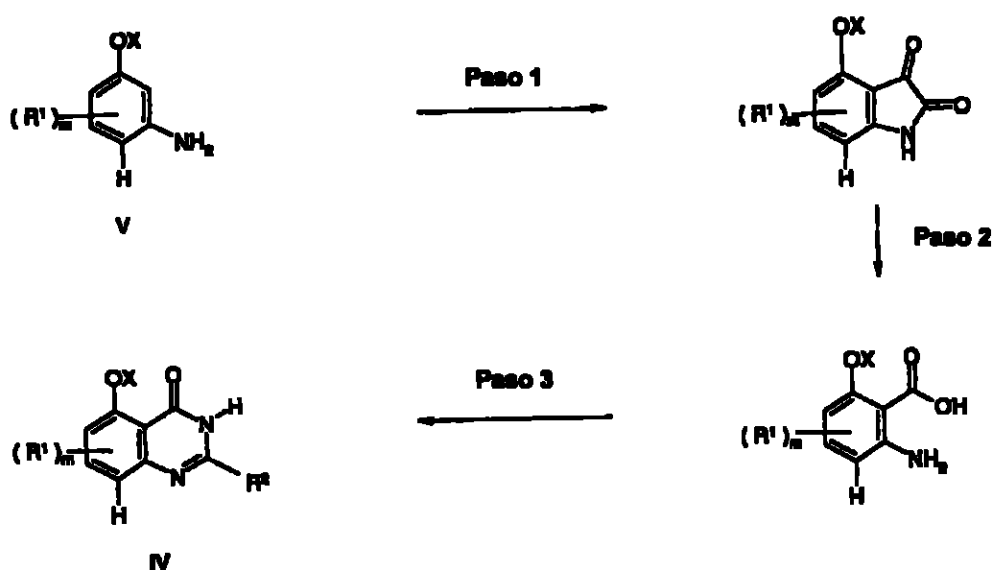
deshidratante apropiado. Condiciones adecuadas para la reacción de acoplamiento se describen más adelante con referencia al proceso (b).

Paso (4)

El grupo protector Pg puede retirarse usando métodos tradicionales, por ejemplo cuando Pg es un grupo pivaloiloximetilo, éste puede retirarse tratando el compuesto de fórmula IVc con una solución de amoníaco metanólico.

El compuesto de fórmula IV puede prepararse a partir de una anilina de la Fórmula V como se ilustra en Esquema de Reacción 2.

Esquema de Reacción 2



en donde R^1 , R^2 , m y X son como se define arriba en el texto.

Notas:

Pasos 1 y 2 pueden llevarse a cabo usando condiciones análogas a los procesos descritos en Organic Syntheses, Coll Vol 1, p 327-330; J Org Chem 1969, 34, 3484-3489.

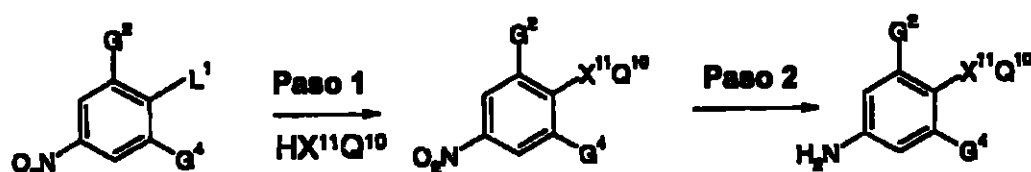
Paso 3 puede llevarse a cabo usando condiciones análogas al proceso descrito en J. Org. Chem. 1952, 17, 141-148; J Med Chem 1994, 37, 2106-2111.

Anilinas de fórmula V son compuestos disponibles en el comercio, o se conocen en la literatura, o pueden prepararse usando procesos bien conocidos en el arte.

Los materiales iniciales de quinazolina de la Fórmula II pueden también prepararse usando rutas sintéticas alternativas a las descritas arriba usando técnicas tradicionales en química orgánica. Ejemplos representativos de métodos sintéticos apropiados para la preparación del material inicial de quinazolina de la Fórmula II y los intermedios descritos arriba en Esquemas de Reacciones 1 y 2 se proporcionan por los ejemplos contenidos aquí.

Compuestos de la Fórmula Q^2LNHR^3 son compuestos disponibles en el comercio, o se conocen en la literatura, o pueden prepararse usando métodos sintéticos tradicionales. Por ejemplo, cuando L es un enlace directo y G^3 es un grupo de la fórmula $-X^{11}-Q^{10}$ el compuesto de la Fórmula Q^2LNHR^3 puede prepararse de acuerdo con Esquema de Reacción 3 o Esquema 4.

Esquema de Reacción 3



en donde X^{11} es, por ejemplo, NR^{20} , O, S ó $NR^{20}C(R^{20})_2$ y G^2 , G^4 , L^1 , Q^{10} y R^{20} son como se define arriba en el texto, excepto que cualquier grupo funcional se protege, si es necesario, y, a partir de entonces, cualquier grupo protector que esté presente se retira por medios tradicionales.

Notas

Paso 1 puede efectuarse bajo condiciones análogas a las usadas en proceso (a) descrito arriba. Los compuestos de la Fórmula $HX^{11}Q^{10}$ se obtienen en el comercio, o se conocen en la literatura, o pueden prepararse usando procesos bien conocidos en el arte.

La reducción del grupo nitro en paso 2 puede llevarse a cabo bajo condiciones estándar, por ejemplo por hidrogenación catalítica sobre un catalizador platino/carbón, paladio/carbón o níquel, tratamiento con un



metal tal como hierro, cloruro de titanio, cloruro de estaño (II) (convenientemente en la presencia de un ácido tal como HCl), o tratamiento con otro agente reductor adecuado tal como ditionito de sodio.

En una variación del proceso (a) la reducción del compuesto nitro en paso 2 de Esquema de Reacción 3 puede llevarse a cabo como se describe arriba, seguida directamente con la reacción con el compuesto de fórmula II en un proceso abreviado, evitando así la necesidad de aislar el compuesto de la Fórmula Q^2LNHR^3 .

Cuando L es un enlace directo y Q^2 es un compuesto de la Fórmula 1a en la cual G^3 es un grupo de la fórmula $-X^{11}-Q^{10}$ en donde X^{11} es O y Q^{10} es heteroaril-(1-6C)alquilo o aril-(1-6C)alquilo, el compuesto de la Fórmula Q^2LNHR^3 puede prepararse, por ejemplo, haciendo reaccionar el compuesto nitro inicial mostrado en Esquema de Reacción 3, en el cual L^1 es OH, con un compuesto de la Fórmula Q^{10} -halogenuro (por ejemplo heteroaril- CH_2 -bromuro o cloruro de bencilo). El grupo nitro puede reducirse entonces a un grupo amino usando paso 2 del proceso en Esquema de Reacción 3. Tales compuestos pueden también prepararse haciendo reaccionar el compuesto nitro inicial mostrado en Esquema de Reacción 3, en el cual L^1 es halogenuro, con un compuesto de la Fórmula $Q^{10}OH$, seguido por la reducción del grupo nitro como se describe arriba en Esquema de Reacción 3.

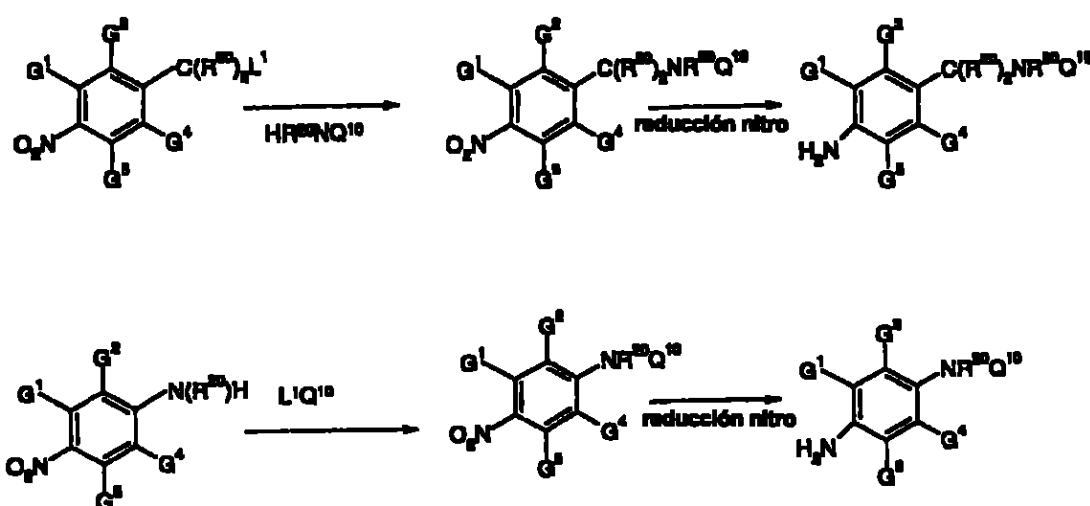
Los compuestos de la fórmula Q^3OH se conocen o pueden prepararse usando métodos conocidos, por ejemplo por reducción del éster correspondiente de la fórmula Q^3COOR , en donde R es, por ejemplo (1-6C)alquilo, o bencilo, con un agente reductor apropiado, por ejemplo borohidruro de sodio.

Cuando L es un enlace directo y Q^2 es un compuesto de la fórmula 1a en el cual G^3 es un grupo de la fórmula $-X^{11}-Q^{10}$ en donde X^{11} es O y Q^{10} es heteroaril-(1-6C)alquilo o aril-(1-6C)alquilo, el compuesto de la fórmula Q^2LNHR^3 puede prepararse, por ejemplo, acoplado el compuesto nitro inicial mostrado en Esquema de Reacción 3, en el cual L^1 es OH, con un compuesto de la fórmula $Q^{10}OH$, convenientemente en la presencia de un

agente deshidratante apropiado. Las condiciones adecuadas para realizar esta reacción son análogas a las descritas más abajo en relación con Proceso (b).

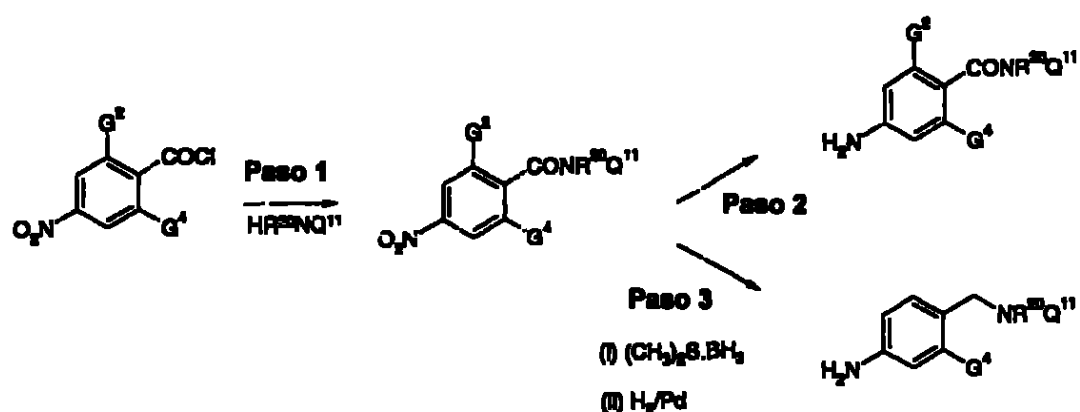
Cuando L es un enlace directo y Q² es un compuesto de la fórmula 1a en el cual G³ es un grupo de la fórmula -X¹¹-Q¹⁰ en donde X¹¹ es C(R²⁰)₂NR²⁰ ó NR²⁰ y Q¹⁰ es heteroaril-(1-6C)alquilo o aril-(1-6C)alquilo, el compuesto de la fórmula Q²LNHR³ puede prepararse, por ejemplo, de acuerdo con Esquema de Reacción 3a:

Esquema de Reacción 3a



en donde Q¹⁰ es heteroaril-(1-6C)alquilo o aril-(1-6C)alquilo, y G¹, G², G⁴, G⁵, L¹ y R²⁰ son como se define más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, y, a partir de entonces, se retira por medios tradicionales cualquier grupo protector que se halle presente. El primer paso de Esquema de Reacción 3a puede efectuarse bajo condiciones análogas a las usadas en proceso (a) descrito arriba. Los compuestos nitro iniciales y los compuestos de la fórmula Q¹⁰NR²⁰H y Q¹⁰L¹ se obtienen en el comercio, o se conocen en la literatura, o pueden prepararse usando procesos bien conocidos en el arte. La reducción del grupo nitro en paso 2 puede llevarse a cabo bajo condiciones análogas a las descritas arriba para Esquema de Reacción 3.

Esquema de Reacción 4



en donde G^2 , G^4 , Q^{11} y R^{20} son como se definen más arriba en el texto, excepto que, si es necesario, se protege cualquier grupo funcional, y, a partir de entonces, se retira por medios tradicionales cualquier grupo protector que se halle presente, y L^1 es un grupo saliente apropiado tal como halogenuro, por ejemplo cloro.

Notas

Apropiadas para la preparación de aquellos compuestos en donde X^{11} es CO ó CH_2NR^{20} .

Paso 1 puede llevarse a cabo bajo condiciones análogas a las usadas en proceso (a) descrito arriba.

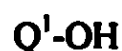
La reducción del grupo nitro en paso 2 puede llevarse a cabo como se describe arriba en Esquema de Reacción 3.

Cuando L es un enlace directo y Q^2 es un compuesto de la fórmula Ia en el cual G^3 es un grupo de la fórmula $-X^{11}-Q^{10}$ en donde X^{11} es CO y Q^{10} es un grupo heterocíclico, que contiene nitrógeno, enlazado a X^{11} por un átomo de nitrógeno, el compuesto de la fórmula Q^2NHR^3 puede prepararse acoplando el compuesto nitro inicial mostrado en Esquema de Reacción 3, en el cual L^1 es carboxi, con un compuesto de la fórmula $Q^{10}H$ en la presencia de un agente acoplante adecuado, por ejemplo O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluoro-fosfato (HATU). Condiciones adecuadas para esta reacción son análogas a las descritas en relación con proceso (i) más adelante.

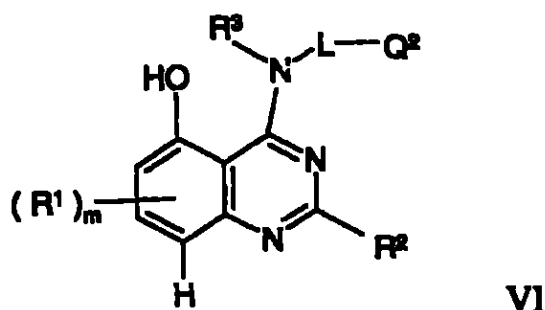
Proceso (b) Para la producción de aquellos compuestos de la fórmula I en donde Z es un átomo de oxígeno, el acoplamiento, convenientemente en la presencia de un agente deshidratante apropiado, de un alcohol de la

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fórmula



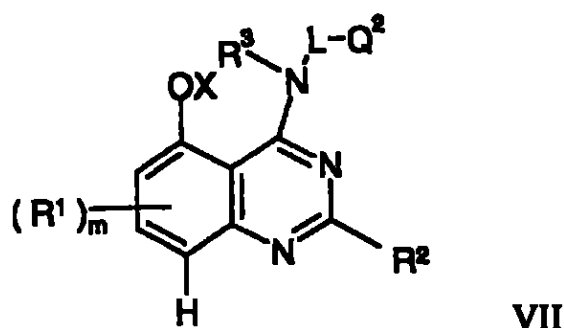
en donde Q^1 tiene cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional con una quinazolina de la fórmula VI



en donde m , R^1 , R^2 , R^3 , L y Q^2 tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales.

Un agente deshidratante apropiado es, por ejemplo, un reactivo de carbodiimida tal como dicitohexilcarbodiimida o 1-(3-dimetilaminopropil)-3-etilcarbodiimida o una mezcla de un compuesto azo tal como azodicarboxilato dietílico o di-tert-butílico y una fosfina tal como trifenilfosfina. La reacción se lleva convenientemente a cabo en la presencia de un solvente o diluyente inerte apropiado, por ejemplo un solvente halogenado tal como cloruro de metileno, cloroformo o tetracloruro de carbono y a una temperatura en el rango, por ejemplo, 0 a 150°C, preferiblemente a temperatura ambiente, o cerca de ella.

La quinazolina de la fórmula VI puede obtenerse por procedimientos tradicionales. Por ejemplo, por escisión del grupo representado por X a partir del compuesto de la fórmula VII



en donde X es como se define más arriba en el texto y m, R¹, R², R³, Q², m y L tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales.

La reacción de escisión se lleva convenientemente a cabo como se describe más arriba en el texto en relación con paso (1) en Esquema de Reacción 1.

El compuesto de Fórmula VII puede prepararse, por ejemplo, haciendo reaccionar el compuesto de la fórmula (IV) como se define más arriba en el texto, con un agente halogenante tal como cloruro de tionilo, cloruro de fosforilo o una mezcla de tetracloruro de carbono y trifenilfosfina. El compuesto resultante se hace reaccionar luego con un compuesto de la fórmula



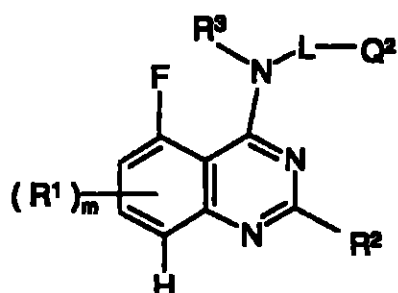
en donde Q², L y R³ tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales. La reacción de halogenación puede realizarse bajo condiciones análogas a las descritas arriba en relación con la reacción con el compuesto de la fórmula III. La reacción subsiguiente con el compuesto de la fórmula Q²LNHR³ puede realizarse bajo condiciones análogas a las descritas arriba en relación con la reacción con el compuesto de la fórmula II.

Proceso (c) Para la producción de aquellos compuestos de la fórmula I en donde Z es O, la reacción [se lleva a cabo], convenientemente en la presencia de una base apropiada, de un alcohol de la fórmula



en donde Q¹ tiene cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional con una quinazolina de la fórmula VIII

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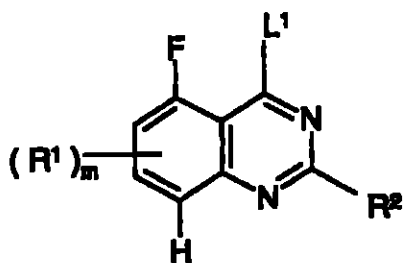
VII

en donde m , R^1 , R^2 , R^3 , L y Q^2 tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales.

Una base apropiada incluye, por ejemplo una base fuerte no nucleófila tal como un hidruro de metal alcalino, por ejemplo hidruro de sodio, o una amida de metal alcalino, por ejemplo di-isopropilamida de litio (LDA).

La reacción se lleva convenientemente a cabo en la presencia de un solvente o diluyente inerte apropiado, por ejemplo un solvente halogenado tal como cloruro de metileno, cloroformo o tetracloruro de carbono, un éter tal como tetrahidrofurano o 1,4-dioxano, un solvente orgánico tal como tolueno, o un solvente aprótico dipolar tal como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidin-2-ona o dimetilsulfóxido. La reacción se lleva convenientemente a cabo a una temperatura en el rango, por ejemplo, 10 a 250°C, preferiblemente en el rango 40 a 150°C. Este proceso se adapta particularmente a la preparación de aquellos compuestos de fórmula I en la cual $m=0$.

La quinazolina de la fórmula VIII puede obtenerse por procedimientos tradicionales. Por ejemplo, una quinazolina de la fórmula IX



IX

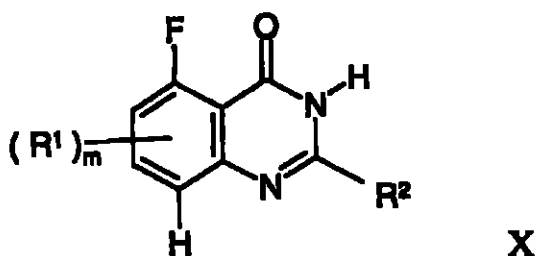
en donde L^1 es un grupo desplazable como se define más arriba en el

texto (tal como halógeno, por ejemplo cloro) y m, R¹ y R² tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, puede hacerse reaccionar con un compuesto de la fórmula



en donde Q², L y R³ tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales. La reacción puede realizarse bajo condiciones análogas a las descritas arriba bajo Proceso (a).

La quinazolina de fórmula IX puede obtenerse usando métodos tradicionales, por ejemplo a 3,4-dihidroquinazolin-4-ona de fórmula X



en donde m, R¹ y R² tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, puede hacerse reaccionar con un agente halogenante tal como cloruro de tionilo, cloruro de fosforilo o una mezcla de tetracloruro de carbono y trifenilfosfina, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales.

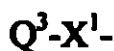
Convenientemente, los compuestos de fórmula VIII pueden prepararse en forma directa a partir del compuesto de Fórmula X usando un proceso abreviado. En este proceso la 3,4-dihidroquinazolin-4-ona de fórmula X se halogena, como se describe arriba, usando un agente halogenante apropiado. El producto resultante se hace reaccionar luego en forma directa con el compuesto de la fórmula Q²LNHR³ como se describe arriba, para proporcionar un compuesto de la fórmula VIII. Este proceso permite preparar compuestos de fórmula VIII sin aislar el compuesto intermedio de la fórmula IX.

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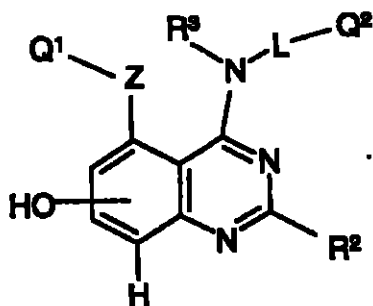
Los materiales iniciales de la quinazolina de fórmula X se conocen o pueden prepararse usando métodos tradicionales. Por ejemplo el compuesto de la fórmula X en donde $m=0$ se describe en J. Org. Chem. 1952, 17,164-176.

En un proceso alternativo la 3,4-dihidroquinazolin-4-ona de fórmula X se hace reaccionar con el alcohol de la fórmula Q^1-OH como se describe arriba para proporcionar un compuesto de fórmula III. El compuesto de Fórmula III puede convertirse entonces en un compuesto de fórmula I por halogenación y reacción con el compuesto de la fórmula Q^2LNHR^3 como se describe arriba bajo Proceso (a).

Proceso (d) Para la producción de aquellos compuestos de la fórmula I en donde m es 1 y R^1 es un grupo de la fórmula



en donde Q^3 es un grupo aril-(1-6C)alquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroaril-(1-6C)alquilo o heterociclíl-(1-6C)alquilo y X^1 es O, el acoplamiento, convenientemente en la presencia de un agente deshidratante apropiado, como se define más arriba en el texto, de una quinazolina de la fórmula XI



XI

en donde Q^1 , Z, L, R^2 , R^3 y Q^2 tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, con un alcohol de la fórmula Q^3OH en donde cualquier grupo funcional en Q^3 se protege, si es necesario, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales.

La reacción se lleva convenientemente a cabo en la presencia de un

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solvente o diluyente inerte apropiado, por ejemplo un solvente halogenado tal como cloruro de metileno, cloroformo o tetracloruro de carbono y a una temperatura en el rango, por ejemplo, 10 a 150°C, preferiblemente a temperatura ambiente, o cerca de ella.

El compuesto de Fórmula XI puede prepararse, por ejemplo, de acuerdo con proceso (a) descrito arriba.

Proceso (e) Para la producción de aquellos compuestos de la fórmula I en donde R¹ es un grupo hidroxilo, la escisión de un derivado de quinazolina de la fórmula I en donde R¹ es un grupo (1-6C)alcoxi o arilmetoxi.

La reacción de escisión puede llevarse convenientemente a cabo por cualquiera de los muchos procedimientos conocidos para una transformación semejante. La reacción de escisión de un compuesto de la fórmula I en donde R¹ es un grupo (1-6C)alcoxi puede llevarse a cabo, por ejemplo, por tratamiento del derivado de quinazolina con un (1-6C)alquilsulfuro de metal alcalino tal como etanotiolato de sodio o, por ejemplo, por tratamiento con un diarilfosfuro de metal alcalino como difenilfosfuro de litio. Alternativamente la reacción de escisión puede llevarse convenientemente a cabo, por ejemplo, por tratamiento del derivado de quinazolina con un trihalogenuro de boro o aluminio tal como tribromuro de boro. La reacción de escisión de un compuesto de la fórmula I en donde R¹ es un grupo arilmetoxi puede llevarse a cabo, por ejemplo, por hidrogenación del derivado de quinazolina en la presencia de un catalizador metálico apropiado tal como paladio o por reacción con un ácido orgánico o inorgánico, por ejemplo ácido trifluoroacético. Tales reacciones se llevan preferiblemente a cabo en la presencia de un solvente o diluyente inerte apropiado como se define más arriba en el texto y a una temperatura en el rango, por ejemplo, 10 a 150°C, preferiblemente a temperatura ambiente, o cerca de ella.

Proceso (f) Para la producción de aquellos compuestos de la fórmula I en donde Q¹, R¹ ó Q² contiene un grupo amino primario o secundario, la escisión del compuesto correspondiente de fórmula I en donde Q¹, R¹ ó Q² contiene un grupo amino primario o secundario protegido.

Grupos protectores apropiados para un grupo amino son, por ejemplo, cualquiera de los grupos protectores divulgados más arriba en el texto para un grupo amino. Métodos adecuados para la escisión de tales grupos protectores amino se divulgan también más arriba en el texto. En particular, un grupo protector apropiado es un grupo alcoxicarbonil inferior tal como un grupo tert-butoxicarbonilo que puede escindirse bajo condiciones de reacción tradicionales tales como bajo hidrólisis catalizada por ácido, por ejemplo en la presencia de ácido trifluoroacético.

Proceso (g) Para la producción de aquellos compuestos de la fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo (1-6C)alcoxi o (1-6C)alcoxi sustituido o un grupo (1-6C)alquilamino o (1-6C)alquilamino sustituido, la alquilación, convenientemente en la presencia de una base apropiada como se define más arriba en el texto, de un derivado de quinazolina de la fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo hidroxilo o un grupo amino primario o secundario, según sea apropiado.

Un agente alquilante apropiado es, por ejemplo, cualquier agente conocido en el arte para la alquilación de hidroxilo a alcoxi o alcoxi sustituido, o para la alquilación de amino a alquilamino o alquilamino sustituido, por ejemplo un halogenuro de alquilo o alquilo sustituido, por ejemplo un cloruro de (1-6C)alquilo, bromuro o yoduro, un cloruro de (1-6C)alquilo sustituido, bromuro o yoduro, o un (1-6C)alquil-tosilato sustituido, convenientemente en la presencia de una base apropiada como se define más arriba en el texto, en un solvente o diluyente inerte apropiado como se define más arriba en el texto y a una temperatura en el rango, por ejemplo, 10 a 140°C, convenientemente a temperatura ambiente, o cerca de ella. Puede usarse un procedimiento análogo para introducir grupos (2-6C)alquenilo opcionalmente sustituidos, (2-6C)alquenilamino, (2-6C)alquinilo o (2-6C)alquinilamino en Q^1 , R^1 ó Q^2 .

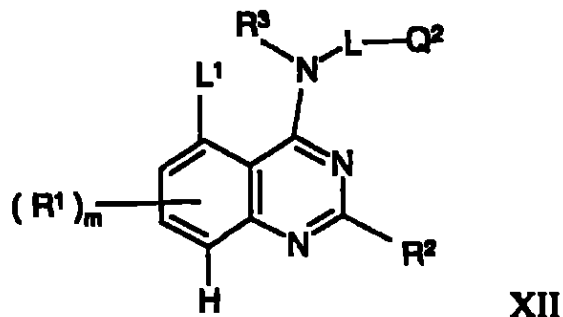
Proceso (h) Para la producción de aquellos compuestos de la fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo (1-6C)alcoxi amino-hidroxidisustituido (tal como 2-hidroxil-3-piperidinopropoxi, 2-hidroxil-3-metilaminopropoxi, 3-dimetilamino-2-hidroxipropoxi o

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3-[N-(3-dimetilaminopropil)-N-metilamino]-2-hidroxi-propoxi), la reacción de un compuesto de la fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo (1-6C)alcoxi epoxi-sustituido con un compuesto heterociclilo o una amina apropiada.

La reacción se lleva convenientemente a cabo en la presencia de diluyente o transportador inerte apropiado como se define más arriba en el texto y a una temperatura en el rango 10 a 150°C, preferiblemente a temperatura ambiente, o cerca de ella.

Proceso (i) La reacción, convenientemente en la presencia de una base apropiada como se define más arriba en el texto, de una quinazolina de la fórmula XII



en donde L^1 es un grupo desplazable como se define más arriba en el texto y m , R^1 , R^2 , R^3 y Q^2 tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, con un compuesto de la fórmula



en donde Q^1 y Z tienen cualquiera de los significados definidos más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales.

La reacción se lleva convenientemente a cabo en la presencia de una base apropiada, tal como un hidruro de metal alcalino, por ejemplo hidruro de sodio.

La reacción se lleva convenientemente a cabo en la presencia de un diluyente o transportador inerte apropiado como se define más arriba en el texto y a una temperatura en el rango 10 a 150°C, preferiblemente a 50°C,

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o cerca.

El compuesto de Fórmula XII puede prepararse usando un procedimiento análogo al descrito para la preparación de fórmula VIII, excepto que el átomo 5-fluoro se reemplaza por L¹.

Proces (j) Para la producción de aquellos compuestos de la fórmula I en donde Q¹, R¹ ó Q² contiene un grupo (1-6C)alcoxi amino-sustituido (tal como 3-piperidinopropoxi, 3-metilaminopropoxi ó 3-dimetilaminopropoxi), la reacción de un compuesto de la fórmula I en donde Q¹, R¹ ó Q² contiene un grupo (1-6C)alcoxi halógeno-sustituido con compuesto heterociclilo o una amina apropiada.

La reacción se lleva convenientemente a cabo en la presencia de un diluyente o transportador inerte apropiado como se define más arriba en el texto y a una temperatura en el rango 10 a 150°C, preferiblemente a temperatura ambiente, o cerca de ella.

Proceso (k) Para la producción de aquellos compuestos de la fórmula I en donde un grupo heterociclilo en R¹, Q¹ ó Q³ contiene un S- o N-óxido, la oxidación de un anillo N o átomo S en un compuesto de la fórmula (I). Agentes oxidantes adecuados incluyen, por ejemplo, un perácido (tal como ácido m-cloroperbenzoico) o ácido perftálico. La oxidación se lleva convenientemente a cabo en un solvente o diluyente inerte apropiado (tal como diclorometano) a una temperatura apropiada (tal como -5 a 50°C).

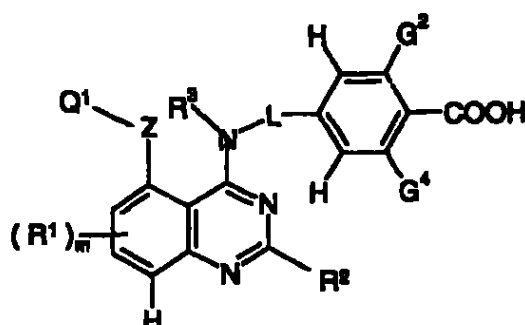
Proceso (l) Para la producción de aquellos compuestos de la fórmula I en donde Q² es un grupo de la fórmula 1a como se define más arriba en el texto y:

(i) G³ es un grupo de la fórmula CON(R²⁰)Q¹⁰ en donde R²⁰ y Q¹⁰ son como se definen más arriba en el texto, o

(ii) G³ es un grupo de la fórmula COQ¹⁰ y Q¹⁰ es un grupo heterociclilo enlazado a nitrógeno,

el acoplamiento de la correspondiente quinazolina carboxi sustituida de la fórmula XIII

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XIII

o un derivado reactivo del mismo, con una amina de la fórmula $\text{NH}(\text{R}^{20})\text{Q}^{10}$ ó Q^{10}H (cuando Q^{10} es un grupo heterociclilo que contiene nitrógeno, por ejemplo homopiperidina) según sea apropiado, en donde R^1 , R^2 , R^3 , R^{20} , Q^1 , Q^{10} , Z , L , m , G^2 y G^4 son como se define más arriba en el texto excepto que se protege, si es necesario, cualquier grupo funcional, a partir de lo cual cualquier grupo protector, que se halle presente, se retira por medios tradicionales. La reacción de acoplamiento se lleva convenientemente a cabo en la presencia de un agente acoplante adecuado, tal como una carbodimida, o un agente de acoplamiento peptídico adecuado, por ejemplo O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio hexafluoro-fosfato. La reacción de acoplamiento se lleva convenientemente a cabo en un solvente inerte tal como 1-metil-2-pirrolidinona, preferiblemente en la presencia de una base apropiada, tal como una amina orgánica, por ejemplo di-isopropiletilamina.

Por 'derivado reactivo' de un compuesto por la fórmula XI se da a entender un derivado de ácido carboxílico de fórmula XI que reaccionará con la amina para proporcionar la amida correspondiente amida. Tales derivados reactivos incluyen, por ejemplo, un cloruro de ácido del compuesto de Fórmula XI.

El compuesto de Fórmula XIII puede prepararse usando proceso (a) de arriba haciendo reaccionar un compuesto de la fórmula II con una anilina apropiada carboxi-sustituída.

Proceso (m) Para la producción de aquellos compuestos de la fórmula I en donde G^3 en Q^2 es un grupo de la fórmula OQ^{10} en donde Q^{10} es aril(1-6C)alquilo, heteroaril(1-6C)alquilo, o heteroarilo, la reacción del compuesto



de fórmula I en donde G^3 en Q^2 es OH con un compuesto de la fórmula Q^{10} - L^1 en donde L^1 es un grupo desplazable, y Q^{10} es como se define más arriba en el texto excepto que, si es necesario, se protege cualquier grupo funcional, y, a partir de entonces, se retira por medios tradicionales cualquier grupo protector que se halle presente. Grupos desplazables adecuados son, por ejemplo halogeno tal como cloro, o alcanosulfoniloxi, tal como mesiloxi. La reacción se lleva convenientemente a cabo en un solvente inerte tal como (sic) o un solvente aprótico dipolar por ejemplo N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidin-2-ona o dimetilsulfóxido. La reacción se lleva convenientemente a cabo en la presencia de una base apropiada, tal como un carbonato de metal alcalino, por ejemplo carbonato de potasio. Generalmente la reacción se realiza a una temperatura de desde -10 a 120°C, convenientemente a temperatura ambiente, o cerca de ella.

Proceso (n) Para la producción de aquellos compuestos de la fórmula I en donde cualquiera de Q^1 , R^1 o Q^2 contiene un grupo (2-6C)alcanoilamino, (2-6C)alcanoilamino sustituido, la acilación de un derivado de quinazolina de la fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo amino. Un agente acilante adecuado es, por ejemplo, cualquier agente conocido en el arte para la acilación de amino a acilamino, por ejemplo un halogenuro de acilo, por ejemplo un cloruro de (2-6C)alcanoilo o bromuro, convenientemente en la presencia de una base apropiada, como se define más arriba en el texto, un anhídrido de ácido alcanoico o anhídrido mixto, por ejemplo un anhídrido de ácido (2-6C)alcanoico tal como anhídrido acético o el anhídrido mixto formado por la reacción de un ácido alcanoico y un halogenuro de (1-4C)alcoxycarbonilo, por ejemplo un cloruro de (1-4C)alcoxycarbonilo, en la presencia de una base apropiada como se define más arriba en el texto. En general, la acilación se lleva a cabo en un solvente o diluyente inerte apropiado como se define más arriba en el texto y a una temperatura, en el rango, por ejemplo, -30°C a 120°C, convenientemente a temperatura ambiente, o cerca de ella.

Puede usarse un proceso análogo para preparar compuestos de la



fórmula I en donde, en lugar del halogenuro de acilo, se utiliza un grupo (1-6C)alcanosulfonilamino o un grupo alcanosulfonilamino sustituido, excepto el (1-6C)alcanosulfonilhalogenuro correspondiente o el alcanosulfonilhalogenuro sustituido (por ejemplo cloruro de metanosulfonilo).

Proceso (o) Para la producción de aquellos compuestos de la fórmula I en donde R^1 , Q^1 ó Q^2 contiene un grupo (1-6C)alquilamino o (1-6C)alquilamino sustituido o un grupo heterociclilo enlazado a nitrógeno, la aminación reductora de un grupo aldehído o cetónico en un compuesto de fórmula I, con un grupo (1-6C)alquilamina, (1-6C)alquilamina sustituida o un heterociclo que contiene un grupo NH en la presencia de un agente reductor apropiado. Un agente reductor apropiado es, por ejemplo, un agente reductor hidruro, por ejemplo un hidruro de aluminio de metal alcalino tal como hidruro de aluminio de litio, ácido fórmico o, preferiblemente, un borohidruro de metal alcalino tal como borohidruro de sodio, cianoborohidruro de sodio, trietilborohidruro de sodio, trimetoxiborohidruro de sodio y triacetoxiborohidruro de sodio. La reacción se realiza convenientemente en un solvente o diluyente inerte apropiado, por ejemplo tetrahidrofurano o éter dietílico para los agentes reductores más poderosos tales como hidruro de aluminio de litio, y, por ejemplo, cloruro de metileno o un solvente prótico tal como metanol y etanol para los agentes reductores menos poderosos tales como triacetoxiborohidruro de sodio y cianoborohidruro de sodio. La reacción se efectúa convenientemente a una temperatura en el rango, por ejemplo, 10 a 100°C, convenientemente a temperatura ambiente, o cerca de ella.

Una aminación reductora análoga a la descrita arriba puede usarse para introducir un grupo alquilo o alquilo sustituido en un grupo amina primario o secundario en un compuesto de la fórmula I por aminación reductora con una cetona correspondiente en la presencia de un agente reductor adecuado. Por ejemplo, para la producción de aquellos compuestos de la fórmula I en donde Q^1 ó Q^2 contiene un grupo N-metilo, el compuesto correspondiente que contiene un grupo NH puede hacerse

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reaccionar con formaldehído en la presencia de un agente reductor adecuado como se describe arriba.

Proceso (p) La conversión de un compuesto de la fórmula I en otro compuesto de la fórmula I.

Se notará que algunos de los distintos sustituyentes de anillo en los compuestos de la presente invención pueden introducirse por reacciones de sustitución aromática estándar o generarse por modificaciones tradicionales de grupo funcional bien sea antes o inmediatamente después de los procesos ya mencionados (por ejemplo como en el proceso (r)), y, como tales, se incluyen en el aspecto de los procesos de la invención. Tales reacciones y modificaciones incluyen, por ejemplo, la introducción de un sustituyente por medio de una reacción de sustitución aromática, reducción de sustituyentes, alquilación de sustituyentes y oxidación de sustituyentes. Los reactivos y las condiciones de reacción para tales procedimientos son bien conocidos en el arte químico. Ejemplos particulares de reacciones de sustitución aromática incluyen la introducción de un grupo nitro usando ácido nítrico concentrado, la introducción de un grupo acilo usando, por ejemplo, un halogenuro de acilo y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; la introducción de un grupo alquilo usando un halogenuro de alquilo y ácido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts; y la introducción de un grupo halógeno. Ejemplos particulares de modificaciones incluyen la oxidación de alquiltio a alquilsulfinilo o alquilsulfonilo; la sustitución de un grupo NH en Q¹ ó Q² por la reacción con un halogenuro de alquilo opcionalmente sustituido, o halogenuro de alquenilo opcionalmente sustituido, un halogenuro de alquinilo opcionalmente sustituido o halogenuro de alcanilo opcionalmente sustituido; la introducción de un grupo halógeno en un anillo aromático o heteroaromático (por ejemplo en un indol) por reacción con una N-halógeno-succinimida; y la introducción de un grupo ciano en un anillo aromático por reacción con un isocianato, por ejemplo clorosufonilisocianato.

Cuando se requiere una sal farmacéuticamente aceptable de un

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derivado de quinazolina de la fórmula I, por ejemplo una sal de adición de ácido, ésta puede obtenerse por, por ejemplo, reacción de dicho derivado de quinazolina con un ácido apropiado usando un procedimiento tradicional.

Análisis Biológicos

Las actividades inhibitoras de los compuestos se evaluaron en análisis de proteína tirosina cinasa no basados en células, así como en análisis de proliferación basados en células, antes de que se evaluara su actividad *in vivo* en estudios de xenoinjerto.

a) Análisis de Fosforilación de Proteína Tirosina Cinasa

Esta prueba mide la capacidad de un compuesto de prueba de inhibir la fosforilación de un sustrato polipéptido que contiene tirosina por una enzima seleccionada de la cinasa EGFR, cinasa erbB2 y cinasa erbB4.

Fragmentos intracelulares recombinantes de EGFR, erbB2 y erbB4 (números de acceso X00588, X03363 y L07868 respectivamente) se clonaron y se expresaron en el sistema baculovirus/Sf21. Se prepararon lisados de estas células por tratamiento con tampón de lisis helado (20mM ácido N-2-hidroxiethylpiperizino-N'-2-etanosulfónico (HEPES) pH7.5, 150mM NaCl, 10% glicerol, 1% Triton X-100, 1.5mM MgCl₂, 1mM etilen glicol-bis(β-aminoetil éter) ácido N',N',N',N'-tetraacético (EGTA), más inhibidores de proteasa y luego se depuran por centrifugación.

La actividad cinasa constitutiva de estas proteínas recombinantes se determinó por su capacidad de fosforilar un péptido sintético (compuesto por un copolímero aleatorio de ácido glutámico, alanina y tirosina en la proporción de 6:3:1). Específicamente, inmunoplasacas Maxisorb™ de 96 pozos se recubrieron con péptido sintético (0.2μg de péptido en 200μl de una solución salina tamponada con fosfato (PBS) e incubada a 4°C durante la noche). Las placas se lavaron en 50mM HEPES pH 7.4 a temperatura ambiente para retirar cualquier exceso de péptido sintético no enlazado. Se evaluaron las actividades EGFR, erbB2 ó erbB4 por incubación en placas recubiertas con péptido durante 20 minutos a temperatura ambiente en 100mM HEPES pH 7.4 a temperatura ambiente, adenosina trifosfato (ATP) a concentración Km para la enzima respectiva, 10mM MnCl₂, 0.1mM Na₃

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VO₄, 0.2mM DL-ditiotreitol (DTT), 0.1% Triton X-100 con el compuesto de prueba en DMSO (concentración final de 2.5%). Las reacciones se terminaron por el retiro de los componentes líquidos del análisis seguido por el lavado de las placas con PBS-T (salina tamponada con fosfato con 0.5% Tween 20).

El producto fosfo-péptido inmovilizado de la reacción se detectó por métodos inmunológicos. En primer término, las placas se incubaron durante 90 minutos a temperatura ambiente con anticuerpos primarios de anti-fosfotirosina que se criaron en el ratón (4G10 de Upstate Biotechnology). Luego de un lavado extensivo, las placas se trataron con anticuerpo secundario anti-ratón de oveja (NXA931 de Amersham) conjugado con peroxidasa de rábano (HRP) durante 60 minutos a temperatura ambiente. Después de un lavado adicional, se midió colorimétricamente la actividad HRP en cada pozo de la placa usando 22'-azino-di-[3-etilbenztiazolina sulfonato (6)] cristales de sal diamonio (ABTS™ de Roche) como sustrato.

La cuantificación del desarrollo de color y, en consecuencia, de actividad enzimática se logró mediante la medición de absorbencia a 405nm en un lector de microplaca ThermoMax de Molecular Devices. La inhibición de cinasa para un compuesto dado se expresó como un valor IC₅₀. Éste se determinó por el cálculo de la concentración de compuesto que se requería para producir una inhibición del 50% de fosforilación en este análisis. El rango de fosforilación se calculó de los valores de control positivo (vehículo más ATP) y negativo (vehículo menos ATP).

b) Análisis de Proliferación de Células KB

Este análisis mide la capacidad de un compuesto de prueba de inhibir la proliferación de células KB (carcinoma naso-faríngeo humano obtenido de la American Type Culture Collection (ATCC)).

Células KB (carcinoma naso-faríngeo humano obtenido de la ATCC se cultivaron en Dulbecco's modified Eagle's medium (DMEM) que contenían 10% suero fetal bovino, 2 mM glutamina y aminoácidos no esenciales a 37°C en un incubador de aire 7.5% CO₂. Se recolectaron las

células de los frascos patrón usando tripsina/ácido etilaminadiaminatetraacético (EDTA). Se midió la densidad celular usando un hemocitómetro y la viabilidad se calculó usando solución *trypan blue* antes de sembrarse a una densidad de 1.25×10^3 células por pozo de una placa de 96 pozos en DMEM que contenía 2.5% suero filtrado con carbón, 1mM glutamina y aminoácidos no esenciales a 37°C en 7.5% CO₂ y se dejaron sedimentar durante 4 horas.

Luego de la adhesión a la placa, las células se tratan con o sin EGF (concentración final de 1ng/ml) y con o sin compuesto en un rango de concentraciones en dimetilsulfóxido (DMSO) (1% final) antes de la incubación durante 4 días. Luego del período de incubación, se determinaron los números de células por retiro del medio por aspiración e incubación con 50µl de bomuro de 3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolio (MTT) (patrón 5mg/ml) durante 2 horas. A continuación se retiró la solución MTT por aspiración, se dejó secar al aire y se disolvieron las células con la adición de 100µl de DMSO.

Se leyó la absorbencia de estas células solubilizadas a 540nm para cuantificar la biomasa celular. La inhibición de la proliferación se expresó como un valor IC₅₀. Éste se determinó por el cálculo de la concentración de compuesto que se requirió para producir una inhibición del 50% de la proliferación. El rango de proliferación se calculó de los valores de control positivo (vehículo más EGF) y negativo (vehículo menos EGF).

c) Análisis de Proliferación de Células H16N-2

Este análisis mide la capacidad de un compuesto de prueba de inhibir la proliferación de células H16N-2 inducida por heregulina β o EGF. Estas células epiteliales no neoplásicas [que] responden en una forma proliferante a la estimulación con EGF o heregulina β (Ram, G.R. and Ethier, S.P. (1996) *Cell Growth and Differentiation*, 7, 551-561), se aislaron en tejido mamario humano (Band, V. and Sager, R. Tumour progression in breast cancer. In; J. S. Rhim and A. Dritschilo (eds.), *Neoplastic Transformation in human Cell Culture*, pp 169-178. Clifton, NJ: Humana Press, 1991) y se obtuvieron del Dana-Farber Cancer Institute, 44 Binney Street, Boston,

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Massachusetts 02115.

Las células H16N-2 se cultivaron rutinariamente en medio de cultivo (una mezcla 1:1 de medio Gibco F12 y Ham's α MEM que contenía 1% suero bovino fetal, 10mM HEPES, 1 μ g/ml Insulina, 12.5ng/ml EGF, 2.8 μ M Hidrocortisona, 2nM Estradiol, 5 μ M Ácido Ascórbico, 10 μ g/ml Transferrina, 0.1mM Fosfoetanolamina, 15nM Selenita de Sodio, 2mM Glutamina, 10nM Tri-yodo-trinolina, 35 μ g/ml Extracto Pituitario Bovino y 0.1mM Etanolamina) a 37°C en un incubador de aire 7.5% CO₂. Se recolectaron las células de los frascos patrón usando Tripsina/ácido etilaminadiaminatetraacético (EDTA). Se midió la densidad celular usando un hemocitómetro y se calculó la viabilidad usando solución *trypan blue* antes de sembrarlas a una densidad de 1.0x10³ células por pozo de una placa de 96 pozos en el medio ya mencionado a 37°C en 7.5% CO₂ y se dejaron sedimentar durante 72 horas.

Como continuación a esto, las células se privaron de suero durante 24 horas con la adición del medio de privación (una mezcla 1:1 de medio Gibco F12 y Ham's α MEM que contenía, 10mM HEPES, 2nM Estradiol, 5 μ M Ácido Ascórbico, 10 μ g/ml Transferrina, 0.1mM Fosfoetanolamina, 15nM Selenita de Sodio, 2mM Glutamina, y 0.1mM Etanolamina) y se incubaron a 37°C en 7.5% CO₂. Seguidamente las células se trataron con y sin un compuesto en un rango de concentraciones en dimetilsulfóxido (DMSO) (1% final) durante dos horas antes de la adición de ligando exógeno (a una concentración final de 100ng/ml de heregulina β o 5ng/ml de EGF) e incubación con ligando y compuesto durante 4 días a 37°C en 7.5% CO₂.

Luego del período de incubación, se determinaron los números de células retirando el medio por aspiración e incubando con 50 μ l de 3-(4,5-Dimetiltiazol-2-il)-2, bromuro de 5-difeniltetrazolio (MTT) (patrón 5mg/ml) durante 2 horas. A continuación se retiró la solución MTT por aspiración, se dejó secar al aire y las células se disolvieron con la adición de 100 μ l de DMSO.

La absorbencia de estas células solubilizadas se leyó a 540nm para

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cuantificar la biomasa celular. La inhibición de la proliferación se expresó como un valor IC_{50} . Éste se determinó por cálculo de la concentración de compuesto que se requirió para proporcionar 50% inhibición de proliferación. El rango de proliferación se calculó de los valores de control positivos (vehículo más ligando) y negativos (vehículo menos ligando).

d) Análisis de Xenoinjerto LoVo *In vivo*

Este análisis mide la capacidad de un compuesto de prueba de inhibir el crecimiento de un injerto de células tumorales LoVo (adenocarcinoma colorectal obtenido de la ATCC) en ratones atímicos Female Swiss (Alderley Park, genotipo *nu/nu*).

Se criaron y mantuvieron ratones atímicos Female Swiss (genotipo *nu/nu*) en Alderley Park en aisladores de presión negativa (PFI Systems Ltd.). Los ratones se alojaron en una instalación de barrera con ciclos luz/oscuridad de 12 horas y se les suministró alimento y agua *ad libitum*. Todos los procedimientos se llevaron a cabo en ratones con una edad mínima de 8 semanas. Se implantaron xenoinjertos de células tumorales LoVo en el flanco posterior de ratones donantes mediante inyecciones subcutáneas de células 1×10^7 recién cultivadas en 100 μ l de medio libre de suero por animal. El día 5 después del implante, los ratones se aleatorizaron en grupos de 7 antes del tratamiento con compuesto o control de vehículo que se administraron una vez al día a 0.1ml/kg de peso corporal. Se evaluó el volumen del tumor dos veces a la semana mediante medición bilateral con un calibre Vernier, usando la fórmula (longitud x ancho) x $\sqrt{(longitud \times ancho) \times (\pi / 6)}$, en donde la longitud era el diámetro más largo a través del tumor, y el ancho era la perpendicular correspondiente. Se calculó la inhibición del crecimiento desde el inicio del tratamiento por comparación de las variaciones medias en el volumen del tumor para el control y los grupos tratados, y se evaluó la significancia estadística entre los dos grupos usando una prueba *t* de Student.

e) Análisis de Xenoinjerto BT-474 *In vivo*

Este análisis mide la capacidad de un compuesto de prueba de inhibir el crecimiento de un xenoinjerto de células tumorales BT-474 (carcinoma

mamario humano obtenido de Dr Baselga, Laboratorio Recerca Oncologica, Paseo Vall D'Hebron 119-129, Barcelona 08035, España) en ratones atímicos Female Swiss (Alderley Park, genotipo *nu/nu*) (Baselga, J. *et al.* (1998) *Cancer Research*, 58, 2825-2831).

Se criaron y mantuvieron ratones atímicos Female Swiss (genotipo *nu/nu*) en Alderley Park en aisladores de presión negativa (PFI Systems Ltd.). Los ratones se alojaron en una instalación de barrera con ciclos luz/oscuridad de 12 horas y se les suministró alimento y agua *ad libitum*. Todos los procedimientos se llevaron a cabo en ratones con una edad mínima de 8 semanas. Se implantaron xenoinjertos de células tumorales BT-474 en el flanco posterior de ratones donantes mediante inyecciones subcutáneas de células 1×10^7 recién cultivadas en 100 μ l de medio libre con 50% Matrigel por animal. El día 14 después del implante, los ratones se aleatorizaron en grupos de 10 antes del tratamiento con compuesto o control de vehículo que se administraron una vez al día a 0.1ml/kg de peso corporal. Se evaluó el volumen del tumor dos veces a la semana mediante medición bilateral con un calibre Vernier, usando la fórmula (longitud x ancho) x $\sqrt{(longitud \times ancho) \times (\pi/6)}$, en donde la longitud era el diámetro más largo a través del tumor, y el ancho era la perpendicular correspondiente. Se calculó la inhibición del crecimiento desde el inicio del tratamiento por comparación de las variaciones medias en el volumen del tumor para el control y los grupos tratados, y se evaluó la significancia estadística entre los dos grupos usando una prueba *t* de Student.

Aunque las propiedades farmacológicas de los compuestos de la fórmula I varían con el cambio estructural, como es de esperar, en general la actividad que poseen compuestos de la fórmula I puede demostrarse en las siguientes concentraciones o dosis en una o más de las pruebas anteriores (a), (b), (c), (d) y (e):-

Prueba (a):- IC_{50} en el rango, por ejemplo, 0.001 - 10 μ M;

Prueba (b):- IC_{50} en el rango, por ejemplo, 0.001 - 20 μ M

Prueba (c):- IC_{50} en el rango, por ejemplo, 0.001 - 20 μ M

Prueba (d):- actividad en el rango, por ejemplo, 1-200 mg/kg/día;



Prueba (e):- actividad en el rango, por ejemplo, 1-200 mg/kg/día;

No se observó toxicidad fisiológicamente inaceptable en Prueba (d) o (e) con la dosis efectiva para los compuestos probados de la presente invención. En consecuencia, no se esperan efectos toxicológicos adversos cuando un compuesto de fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto, se administran en los rangos de posología definidos más adelante.

De acuerdo con un aspecto adicional de la invención, se provee una composición farmacéutica que comprende un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto en asociación con un diluyente o transportador farmacéuticamente aceptables.

Las composiciones de la invención pueden estar en una forma apropiada para empleo oral (por ejemplo como tabletas, pastillas, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, polvos dispersables o gránulos, jarabes y elixires), para uso local (por ejemplo como cremas, ungüentos, geles, o soluciones acuosas u oleosas o suspensiones), para administración por inhalación (por ejemplo como un polvo finamente dividido o un aerosol líquido), para administración por insuflación (por ejemplo como un polvo finamente dividido) o para administración parenteral (por ejemplo como una solución estéril acuosa u oleosa para administración intravenosa, subcutánea, intramuscular o como un supositorio para administración rectal).

Las composiciones de la invención pueden obtenerse por procedimientos tradicionales usando excipientes farmacéuticos tradicionales, bien conocidos en el arte. Por lo tanto, las composiciones previstas para uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o preservadores.

La cantidad de ingrediente activo, que se combina con uno o más excipientes para producir una forma farmacéutica única, variará necesariamente dependiendo del anfitrión tratado y la vía particular de administración. Por ejemplo, una formulación prevista para administración



oral a humanos contendrá generalmente, por ejemplo, desde 0.5 mg a 0.5 g de agente activo (más convenientemente desde 0.5 a 100 mg, por ejemplo desde 1 a 30 mg) compuesta con una cantidad apropiada y conveniente de excipientes que pueden variar desde alrededor de 5 a alrededor de 98 por ciento en peso de la composición total.

El tamaño de la dosis para propósitos terapéuticos o profilácticos de un compuesto de la fórmula I variará naturalmente de acuerdo con la índole y gravedad de las afecciones, la edad y sexo del animal o paciente y la vía de administración, de acuerdo con principios bien conocidos de medicina.

Al usar un compuesto de la fórmula I para propósitos terapéuticos o profilácticos, éste se administrará generalmente de manera que se reciba una dosis diaria en el rango, por ejemplo, 0.1 mg/kg a 75 mg/kg de peso corporal, dada, si se requiere, en dosis divididas. En general, se administrarán dosis menores cuando se emplee una vía parenteral. Así, por ejemplo, para administración intravenosa, generalmente se empleará una dosis en el rango, por ejemplo, 0.1 mg/kg a 30 mg/kg de peso corporal. De manera similar, para administración por inhalación, se usará una dosis en el rango, por ejemplo, 0.05 mg/kg a 25 mg/kg de peso corporal. No obstante, se prefiere la administración oral, particularmente en forma de tableta. Típicamente, formas farmacéuticas unitarias contendrán alrededor de 0.5 mg a 0.5 g de un compuesto de esta invención.

Hemos encontrado que los compuestos de la presente invención poseen propiedades antiproliferantes tales como propiedades anti-cáncer que se cree que provienen de su actividad inhibidora de tirosina cinasa de receptor de la familia erbB, particularmente la inhibición de las tirosina cinasas de receptor EGFR y/o erbB2 y/o erbB4. En consecuencia, se espera que los compuestos de la presente invención sean útiles en el tratamiento de enfermedades o afecciones médicas mediadas solo o en parte por tirosina cinasas de receptor erbB, i.e. los compuestos pueden usarse para producir un efecto inhibidor de tirosina cinasa de receptor erbB en un animal de sangre caliente necesitado de dicho tratamiento. Por lo tanto, los compuestos de la presente invención proveen un método para el tratamiento

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de células malignas caracterizadas por inhibición de una o más de la familia erbB de tirosina cinasas de receptor. Particularmente, los compuestos de la invención pueden usarse para producir un efecto antiproliferante y/o pro-apoptótico y/o anti-invasivo mediado solo o en parte por la inhibición de tirosina cinasas de receptor erbB. Particularmente, se espera que los compuestos de la presente invención sean útiles en la prevención o tratamiento de aquellos tumores que son sensibles a la inhibición de una o más tirosina cinasas de receptor erbB, tales como cinasa EGFR y/o erbB2 y/o erbB4 que están implicadas en los pasos de transducción de señales que inducen la proliferación y supervivencia de estas células tumorales. En consecuencia, se espera que los compuestos de la presente invención sean útiles en el tratamiento y/o prevención de un número de trastornos hiperproliferantes proveyendo un efecto antiproliferante. Estos trastornos incluyen, por ejemplo psoriasis, hiperplasia prostática benigna (BPH), aterosclerosis y restenosis y, en particular, tumores inducidos por tirosina cinasa de receptor EGF y/o erbB2. Tales tumores benignos o malignos pueden afectar cualquier tejido e incluyen neoplasias hematológicas tales como leucemia, mieloma o linfoma múltiple, y también tumores sólidos, por ejemplo cánceres de los conductos biliares, óseos, de vejiga, de cerebro/CNS, de mama, colorrectales, endometriales, gástricos, de cabeza y cuello, hepáticos, pulmonares, neuronales, esofágicos, ováricos, pancreáticos, de próstata, renales, de piel, testiculares, de tiroides, uterinos y vulvares.

Ciertos compuestos de acuerdo con la presente invención poseen potente actividad inhibidora contra tirosina cinasa EGFR presentando a la vez actividad menos potente contra otras tirosina cinasas de receptor tales como erbB2. Se espera que tales compuestos sean útiles como inhibidores selectivos de tirosina de receptor. Más aún, ciertos compuestos de acuerdo con la presente invención son potentes inhibidores de ambas tirosina cinasas EGFR erbB2 y se espera que sean útiles en el tratamiento de afecciones mediadas por ambas tirosina cinasas EGFR y erbB2.

De acuerdo con este aspecto de la invención se provee un compuesto

de la fórmula I, o una sal farmacéuticamente aceptable del mismo, para uso como un medicamento.

Así, de acuerdo con este aspecto de la invención se provee el uso de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto en la manufactura de un medicamento para uso en la producción de un efecto antiproliferante en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para producir un efecto antiproliferante en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, el cual comprende administrar a dicho animal una cantidad efectiva de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto.

De acuerdo con un aspecto adicional de la invención se provee un compuesto de la fórmula I, o una sal farmacéuticamente aceptable del mismo, para uso en la producción de un efecto antiproliferante en un animal de sangre caliente tal como el hombre.

De acuerdo con un aspecto adicional de la invención se provee el uso de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto en la manufactura de un medicamento para uso en la prevención o tratamiento de aquellos tumores que son sensibles a la inhibición de tirosina cinasas de receptor erbB, tales como EGFR y/o erbB2 y/o erbB4, que están implicadas en los pasos de transducción de señales que llevan a la proliferación de células tumorales.

De acuerdo con una característica adicional este aspecto de la invención se provee un método para la prevención o tratamiento de aquellos tumores que son sensibles a la inhibición de una o más de la familia erbB de tirosina cinasas de receptor, tales como EGFR y/o erbB2 y/o erbB4, que están implicadas en los pasos de transducción de señales, que llevan a la

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proliferación y/o supervivencia de células tumorales en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, el cual comprende administrar a dicho animal una cantidad efectiva de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto.

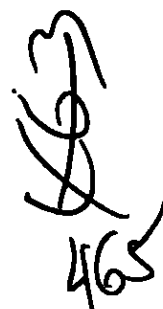
De acuerdo con un aspecto adicional de la invención se provee un compuesto de la fórmula I, o una sal farmacéuticamente aceptable del mismo, para uso en la prevención o tratamiento de aquellos tumores que son sensibles a la inhibición de de una o más de la familia erbB de tirosina cinasas de receptor, tales como EGFR y/o erbB2 y/o erbB4, que están implicadas en los pasos de transducción de señales, que llevan a la proliferación y/o supervivencia de células tumorales.

De acuerdo con un aspecto adicional de la invención se provee el uso de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto, en la manufactura de un medicamento para uso en proveer un efecto inhibidor de cinasa EGFR y/o erbB2 y/o erbB4.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para proveer un efecto inhibidor de cinasa EGFR y/o erbB2 y/o erbB4 en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, el cual comprende administrar a dicho animal una cantidad efectiva de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto.

De acuerdo con un aspecto adicional de la invención se provee un compuesto de la fórmula I, o una sal farmacéuticamente aceptable del mismo, para uso en proveer un efecto inhibidor de cinasa EGFR y/o erbB2 y/o erbB4.

De acuerdo con un aspecto adicional de la invención se provee el uso de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto en la manufactura de un medicamento para uso en proveer un



efecto inhibidor selectivo de cinasa EGFR.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para proveer un efecto inhibidor selectivo de cinasa EGFR en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, el cual comprende administrar a dicho animal una cantidad efectiva de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto.

De acuerdo con un aspecto adicional de la invención se provee un compuesto de la fórmula I, o una sal farmacéuticamente aceptable del mismo, para uso en proveer un efecto inhibidor selectivo de cinasa EGFR.

Por "un efecto inhibidor selectivo de cinasa EGFR " se quiere dar a entender que el derivado de quinazolina de fórmula I es más potente contra la tirosina cinasa EGFR de lo que es contra otras. En particular, el derivado de quinazolina de fórmula I es más potente contra tirosina cinasa EGFR que lo que es contra otras tirosina cinasas de receptor erbB tales como erbB2. Por ejemplo, en un análisis celular (tal como en el análisis H16N-2 descrito aquí) el derivado de quinazolina de fórmula I es por lo menos 5 veces, preferiblemente por lo menos 10 veces más potente contra la proliferación inducida por tirosina cinasa EGFR de lo que es contra la proliferación inducida por la tirosina cinasa erbB2, como se determina de los calores relativos IC_{50} .

De acuerdo con un aspecto adicional de la presente invención se provee el uso de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto, en la manufactura de un medicamento para uso en el tratamiento de un cáncer seleccionado de leucemia, mieloma múltiple, linfoma, cáncer de los conductos biliares, óseo, de la vejiga, del cerebro/CNS, de mama, colorrectal, endometrial, gástrico, de cabeza y cuello, hepático, del pulmón, neuronal, esofágico, ovárico, pancreático, de la próstata, renal, de la piel, testicular, de la tiroides, uterino y vulvar.

De acuerdo con un característica adicional de este aspecto de la

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invención se provee un método para tratar un cáncer seleccionado de leucemia, mieloma múltiple, linfoma, cáncer de los conductos biliares, óseo, de la vejiga, del cerebro/CNS, de mama, colorrectal, endometrial, gástrico, de cabeza y cuello, hepático, del pulmón, neuronal, esofágico, ovárico, pancreático, de la próstata, renal, de la piel, testicular, de la tiroides, uterino y vulvara en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, el cual comprende administrar a dicho animal una cantidad efectiva de un derivado de quinazolina de la fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define más arriba en el texto.

De acuerdo con un aspecto adicional de la invención se provee un compuesto de la fórmula I, o una sal farmacéuticamente aceptable del mismo, para uso en el tratamiento de un cáncer seleccionado de leucemia, mieloma múltiple, linfoma, cáncer de los conductos biliares, óseo, de la vejiga, del cerebro/CNS, de mama, colorrectal, endometrial, gástrico, de cabeza y cuello, hepático, del pulmón, neuronal, esofágico, ovárico, pancreático, de la próstata, renal, de la piel, testicular, de la tiroides, uterino y vulvar.

El tratamiento antiproliferante definido más arriba en el texto puede aplicarse como una terapia única o puede incluir, además del derivado de quinazolina de la invención, cirugía tradicional o radioterapia o quimioterapia. Tal quimioterapia puede incluir una o más de las siguientes categorías de agentes antineoplásicos:-

(i) fármacos antiproliferantes/antineoplásicos y combinaciones de los mismos, como se emplean en la oncología médica, tales como agentes alquilantes (por ejemplo cis-platino, carboplatino, ciclofosfamida, moztaza nitrogenada, melfalan, clorambucil, busulfan y nitrosoureas); antimetabolitos (por ejemplo antifolatos tales como fluoropirimidinas como 5-fluorouracil y tegafur, raltitrexed, metotrexato, citarabina e hidroxiurea; antibióticos antineoplásicos (por ejemplo antraciclinas como adriamicina, bleomicina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicina-C, dactinomicina y mitramicina); agentes antimetabólicos (por

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ejemplo antineoplásicos como vincristina, vinblastina, vindesina y vinorelbina y taxoides como taxol y taxotere); e inhibidores de topoisomerasa (por ejemplo epipodofilotoxinas como etopósido y tenipósido, amsacrina, topotecan y camptotecina);

(ii) agentes citostáticos tales como antioestrógenos (por ejemplo tamoxifeno, toremifeno, raloxifeno, droloxifeno y yodoxifeno), antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas LHRH o agonistas LHRH (por ejemplo goserelina, leuprorelina y buserelina), progestógenos (por ejemplo acetato de megestrol), inhibidores de aromatasa (por ejemplo como anastrozol, letrozol, vorazol y exemestane) e inhibidores de 5 α -reductasa tales como finasteride;

(iii) agentes que inhiben la invasión de células cancerosas (por ejemplo inhibidores de metaloproteínasa como marimastat e inhibidores de la función de receptor activador de plasminógeno tipo urocinasa);

(iv) otros inhibidores de función de factor de crecimiento, por ejemplo tales inhibidores incluyen anticuerpos de factor de crecimiento, anticuerpos de receptor de factor de crecimiento (por ejemplo el anticuerpo anti-erbB2 trastuzumab [Herceptin™] t el anticuerpo anti-erbB1 cetuximab [C225]), inhibidores de farnesiltransferasa, inhibidores de tirosina cinasa e inhibidores de serina/treonina cinasa, por ejemplo inhibidores de la familia de factor de crecimiento epidérmico (por ejemplo inhibidores de tirosina cinasa de la familia EGFR tales como N-(3-cloro-4-fluorofenil)-7-metoxi-6-(3-morfolinopropoxi)quinazolin-4-amina (gefitinib, AZD1839), N-(3-etinilfenil)-6,7-bis(2-metoxietoxi)quinazolin-4-amina (erlotinib, OSI-774) y 6-acrilamido-N-(3-cloro-4-fluorofenil)-7-(3-morfolinopropoxi)quinazolin-4-amina (CI 1033)), por ejemplo inhibidores de la familia de factor de crecimiento derivado de plaquetas y por ejemplo inhibidores de la familia de factor de crecimiento de hepatocitos;

(v) agentes antiangiogénicos tales como los que inhiben los efectos del factor de crecimiento endotelial vascular, (por ejemplo el anticuerpo del factor de crecimiento celular endotelial anti-vascular bevacizumab

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[Avastin™], compuestos tales como los divulgados en las Solicitudes de Patente Internacional WO 97/22596, WO 97/30035, WO 97/32856 y WO 98/13354) y compuestos que funcionan por otros mecanismos (por ejemplo linomida, inhibidores de la función integrina $\alpha v \beta 3$ y angiostatina);

(vi) agentes de lesión vascular tales como combretastatina A4 y compuestos divulgados en las Solicitudes de Patente Internacional WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;

(vii) terapias complementarias, por ejemplo las que se dirigen a las dianas ya enumeradas, tales como ISIS 2503, un complemento anti-ras;

(viii) métodos de genoterapia, incluidos por ejemplo, métodos para reemplazar genes aberrantes tales como p53 aberrante o BRCA1 aberrante o métodos BRCA2, GDEPT (terapia con profármacos enzimáticos direccionados por genes) tales como los que usan deaminasa de citosina, cinasa de timidina o una enzima nitrorreductasa bacteriana y métodos para aumentar la tolerancia del paciente a la quimioterapia o la radioterapia tales como genoterapias de resistencia multi-fármaco; y

(ix) métodos de inmunoterapia, incluidos por ejemplo métodos *ex-vivo* e *in-vivo* para aumentar la inmunogenicidad de células tumorales en el paciente, tales como transfección con citocinas tales como interleucina 2, interleucina 4 o factor estimulante de colonias macrófago-granulocito, métodos para disminuir la anergia de células T, métodos que utilizan células inmunes transfectadas tales como células dendríticas transfectadas con citocina, métodos que utilizan estirpes de células tumorales transfectadas con citosina y métodos que utilizan anticuerpos anti-idiopáticos.

Tal tratamiento conjunto puede lograrse mediante la administración simultánea, consecutiva o separada de los componentes individuales del tratamiento. Tales productos de combinación emplean los compuestos de esta invención en el rango de administración descrito más arriba en el texto y el otro agente farmacéuticamente activo dentro de su rango de administración aprobado.

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De acuerdo con este aspecto de la invención se provee un producto farmacéutico que comprende un derivado de quinazolina de la fórmula I como se define más arriba en el texto y un agente antineoplásico adicional como se define más arriba en el texto para el tratamiento conjunto de cáncer.

Aunque los compuestos de la fórmula I son principalmente útiles como agentes terapéuticos para uso en animales de sangre caliente (incluido el hombre), son también de utilidad, siempre que se requiera, para inhibir los efectos de cinasas de proteína tirosina de receptor erbB. Por lo tanto, son también útiles como estándares farmacológicos para uso en el desarrollo de nuevas pruebas biológicas para la evaluación de los efectos de inhibidores de la actividad del ciclo celular en animales de laboratorio tales como gatos, perros, conejos, monos, ratas y ratones, y en la investigación de nuevos agentes farmacológicos.

La invención se ilustrará ahora por los siguientes ejemplos no limitantes en los cuales, a menos que se indique lo contrario:

- (i) las temperaturas se dan en grados Celsius (°C); las operaciones se llevaron a cabo a la temperatura de la sala o a temperatura ambiente, es decir, a una temperatura en el rango de 18-25°C;
- (ii) las soluciones orgánicas se secaron sobre sulfato de magnesio anhidro; la evaporación del solvente se efectuó usando un evaporador rotatorio bajo presión reducida (600-4000 Pascals; 4.5-30mmHg) con una temperatura de baño de hasta 60°C;
- (iii) cromatografía significa cromatografía de destello en gel de sílice; la cromatografía (TLC) de capa delgada se realizó en placas de gel de sílice;
- (iv) en general, el curso de las reacciones se siguió por TLC y / o LC-MS analítica, y los tiempos de reacción se dan con fines de ilustración únicamente;
- (v) los productos finales presentaron espectros satisfactorios de resonancia magnética nuclear de protones (NMR) y/o datos de espectro de masa;
- (vi) los rendimientos se indican con fines de ilustración únicamente y no son necesariamente los que pueden obtenerse por un desarrollo diligente de

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procesos; las preparaciones se repitieron si se necesitó más material;

(vii) cuando se incluyen, los datos NMR se indican en la forma de valores delta para los principales protones de diagnóstico, dados en partes por millón (ppm) relativas a tetrametilsilano (TMS) como un estándar interno, determinados a 300 MHz usando dimetilsulfóxido de perdeuterio (DMSO- d_6) como solvente a menos que se indique lo contrario; se han usado las siguientes abreviaturas: s, singlete; d, doblete; t, triplete; q, cuartete; m, multiplete; b, amplio;

(viii) los símbolos químicos tienen sus significados habituales; se emplean unidades SI y símbolos;

(ix) las proporciones de solvente se dan en términos de volumen: volumen (v/v); y

(x) los espectros de masas se corrieron con una energía de electrones de 70 voltios electrón en el modo de ionización química (CI) usando una sonda de exposición directa; donde se indica, la ionización se realizó por impacto de electrones (EI), bombardeo de átomos rápidos (FAB) o electroatomización (ESP); se dan los valores de m/z ; generalmente, sólo se reportan los iones que indican la masa original; y a menos que se estipule lo contrario, el ión de masa citado es $(MH)^+$ el cual se refiere a ión de masa protonado; la referencia a M^+ es al ión de masa generado por la pérdida de un electrón; y la referencia a $M-H^+$ es al ión de masa generado por la pérdida de un protón;

(xi) a menos que se declare lo contrario los compuestos que contienen un átomo de carbono asimétricamente sustituido y/o un átomo de azufre no se han resuelto;

(xii) donde se describe una síntesis como análoga a la descrita en un ejemplo previo, las cantidades usadas son los equivalentes de la relación milimolar a los usados en el ejemplo previo;

(xvi) se han utilizado las siguientes abreviaturas:

THF	tetrahidrofurano;
DMF	<i>N,N</i> -dimetilformamida;
DMA	<i>N,N</i> -dimetilacetamida;

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NMP	1-metil-2-pirrolidinona;
DCM	diclorometano;
DMSO	dimetilsulfóxido;
HATU	Hexafluoro-fosfato de O-(7-Azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio;
<i>m</i> -CPBA	Ácido <i>meta</i> -cloroperbenzoico;
IPA	isopropanol; y
Éter	éter dietílico.

xvii) donde se describe una síntesis como conducente a una sal de adición de ácido (verbigracia, sal HCl), no se determinó la estequiometría de la sal. A menos que se especifique lo contrario, todos los datos NMR se reportan sobre material de base libre, con sales aisladas convertidas en la base libre antes de la caracterización, tratando una solución de la sal en metanol acuoso con una base tal como hidróxido de amonio o bicarbonato de sodio, precipitando así la base libre, o por cromatografía en sílice usando un eluyente que contiene una base tal como amoníaco. Alternativamente, la base libre puede obtenerse por un método de extracción en donde el compuesto se divide en porciones entre un solvente orgánico y un medio acuoso básico. La base libre se aísla entonces del medio orgánico, por ejemplo, por evaporación del solvente orgánico.

Ejemplo 1

Clorhidrato de 4-(3-bromoanilino)-7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina

Una mezcla de 4-cloro-7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16) (0.2 g), 3-bromoanilina (0.066 ml) y HCl en dioxano (4M, 0.5 ml) en IPA (3 ml) se calentó a reflujo durante 6 horas. La reacción se enfrió, y el precipitado resultante se filtró, se lavó con IPA y éter, y se secó *in vacuo* para producir el compuesto del título como un sólido amarillo (0.115 g, 43%); Espectro de masa M^+ 527, 525.

El procedimiento descrito arriba se repitió usando la 4-cloroquinazolina apropiada y anilina. Así se obtuvieron los



compuestos descritos a continuación:

Ejemplo 1.1

Clorhidrato de 4-(3-cloroanilino)-7-(3-(R)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido haciendo reaccionar 4-cloro-7-(3-(R)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16) con 3-cloroanilina en 53% de rendimiento; Espectro de masa M^+ 481.

Ejemplo 1.2

Clorhidrato de 4-(3-metilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) con *meta*-toluidina en 25% de rendimiento; Espectro de masa MH^+ 349.

Ejemplo 1.3

Clorhidrato de 4-(3-cloroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) con 3-cloroanilina en 29% de rendimiento; Espectro de masa M^+ 369.

Ejemplo 1.4

Clorhidrato de 4-(3-bromoanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) con 3-bromoanilina en 36% de rendimiento; Espectro de masa M^+ 415,413.

Ejemplo 1.5

Clorhidrato de 4-(3-etinilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) con 3-etinilanilina en 27% de rendimiento; Espectro de masa $M-H^+$ 357.

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Ejemplo 1.6**Clorhidrato de 4-(3-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) con 3-fluoroanilina en 26% de rendimiento; Espectro de masa MH^+ 353.

Ejemplo 1.7**Clorhidrato de 4-(indol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) con 5-aminoindol en 30% de rendimiento; Espectro de masa MH^+ 374.

Ejemplo 1.8**Clorhidrato de 4-(indazol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) con 5-aminoindazol en 30% de rendimiento; Espectro de masa MH^+ 375.

Ejemplo 1.9**Clorhidrato de 4-(3-cloro-4-(azepan-1-ilcarbonil)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) con 4-(azepan-1-ilcarbonil)-3-cloroanilina (Ejemplo de Referencia 29) en 45% de rendimiento; Espectro NMR ($CDCl_3$) 1.50 (bs, 6H), 1.84 (bs, 2H), 1.99 (m, 2H), 2.30 (m, 4H), 2.34 (s, 3H), 2.81 (m, 2H), 3.31 (m, 2H), 3.72 (m, 2H), 3.92 (s, 3H), 4.57 (m, 1H), 6.52 (d, 1H), 6.85 (d, 1H), 7.24 (d, 1H), 7.56 (dd, 1H), 8.09 (d, 1H), 8.61 (s, 1H), 9.99 (s, 1H); Espectro de masa MH^+ 524.

Ejemplo 1.10**Clorhidrato de 4-(3-bromoindol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina**

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Obtenido haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 5-amino-3-bromoindol (Ejemplo de Referencia 25.2) en 19% de rendimiento; Espectro NMR (CDCl_3) 2.06 (m, 2H), 2.22 (m, 2H), 2.33 (s, 3H), 2.40 (m, 2H), 2.75 (m, 2H), 3.92 (s, 3H), 4.65 (m, 1H), 6.51 (d, 1H), 6.83 (d, 1H), 7.22 (d, 1H), 7.35 (d, 1H), 7.47 (dd, 1H), 7.84 (s, 1H), 8.47 (bs, 1H), 8.53 (s, 1H), 9.84 (s, 1H); Espectro de masa MH^+ 482,484.

Ejemplo 1.11

Clorhidrato de 4-(3-cloroindol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) y 5-amino-3-cloroindol (Ejemplo de Referencia 26.2) en 11% de rendimiento; Espectro de masa M^+ 408.

Ejemplo 1.12

Clorhidrato de 4-(3-cianoindol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) con 5-aminoindol-3-carbonitrilo (Ejemplo de Referencia 27.2) en 28% de rendimiento; Espectro NMR (DMSO-d_6) 2.3 (m, 4H), 2.7 (m, 3H), 3.2 - 3.6 (m, 4H) 5.1 (m, 1H), 7.5 (m, 3H), 7.7 (m, 1H), 8.0 (m, 1H), 8.2 (s, 1H), 8.3 (s, 1H), 8.9 (s, 1H); Espectro de masa MH^+ 399.

Ejemplo 2

4-(3-Bromoanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Una solución de ácido clorhídrico en dioxano (4M, 0.5 ml) se agregó a una mezcla de 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) (308 mg) y 3-bromoanilina (172 mg) en dioxano (20 ml). La suspensión resultante se calentó a reflujo durante 4 horas, luego se dejó enfriar a temperatura ambiente. La mezcla de reacción se dividió en porciones entre solución de carbonato hidrogenado de sodio, acuoso, saturado, y DCM.

Los extractos orgánicos combinados se secaron (sulfato de sodio) y se concentraron para proporcionar un aceite anaranjado, el cual se purificó por cromatografía usando 0-5% metanol en DCM como eluyente para proporcionar el compuesto del título como un sólido blanco (190 mg, 43%); Espectro NMR (CDCl_3) 2.10 (m, 2H), 2.38 (m, 4H), 2.42 (s, 3H), 2.90 (m, 2H), 4.00 (s, 3H), 4.66 (m, 1H), 6.60 (d, 1H), 6.93 (d, 1H), 7.31 (m, 2H), 7.65 (m, 1H), 8.22 (m, 1H), 8.68 (s, 1H), 9.98 (s, 1H); Espectro de masa MH^+ 443, 445.

El procedimiento descrito arriba se repitió usando la 4-cloroquinazolina y anilina. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 2.1

4-(3-Cloroindol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 5-amino-3-cloroindol (Ejemplo de Referencia 26.2) en 51% de rendimiento; Espectro NMR (DMSO-d_6) 1.94 (m, 2H), 2.14 (m, 2H), 2.17 (s, 3H), 2.34 (m, 2H), 2.64 (m, 2H), 3.92 (s, 3H), 4.86 (m, 1H), 6.81 (s, 2H), 7.34 (dd, 1H), 7.47 (d, 1H), 7.55 (d, 1H), 9.97 (s, 1H), 11.37 (s, 1H); Espectro de masa MH^+ 438, 440.

Ejemplo 2.2

4-(3-Etinilanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 3-etinilanilina en 41% de rendimiento; Espectro NMR (CDCl_3) 2.10 (m, 2H), 2.28 (m, 4H), 2.35 (s, 3H), 2.83 (m, 2H), 3.10 (s, 1H), 3.93 (s, 3H), 4.59 (m, 1H), 6.53 (d, 1H), 6.85 (d, 1H), 7.24 - 7.36 (m, 2H), 7.76 (d, 1H), 7.94 (d, 1H), 8.59 (s, 1H), 9.90 (s, 1H); Espectro de masa MH^+ 389.

Ejemplo 2.3

4-(Indazol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-

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4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 5-aminoindazol en 28% de rendimiento; Espectro NMR (DMSO-d₆) 1.93 (m, 2H), 2.19 (bs, 4H), 2.32 (t, 2H), 2.63 (m, 2H), 3.91 (s, 3H), 4.84 (m, 1H), 6.82 (s, 2H), 7.52 (d, 1H), 7.59 (d, 1H), 8.10 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H), 13.05 (s, 1H); Espectro de masa MH⁺ 405.

Ejemplo 2.4

4-(3-Cloro-4-fluoroanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 3-cloro-4-fluoroanilina en 31% de rendimiento; Espectro NMR (CDCl₃) 2.00 (m, 2H), 2.31 (m, 7H), 2.80 (m, 2H), 3.92 (s, 3H), 4.58 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.46 (m, 1H), 8.00 (dd, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Espectro de masa MH⁺ 417,419.

Ejemplo 2.5

4-(3-Cloroanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 3-cloroanilina en 36% de rendimiento; Espectro NMR (CDCl₃) 2.01 (m, 2H), 2.30 (m, 7H), 2.81 (m, 2H), 3.92 (s, 3H), 4.57 (m, 1H), 6.52 (d, 1H), 6.85 (d, 1H), 7.08 (m, 1H), 7.28 (t, 1H), 7.51 (dm, 1H), 7.99 (t, 1H), 8.59 (s, 1H), 9.92 (s, 1H); Espectro de masa MH⁺ 399. 401.

Ejemplo 2.6

7-Metoxi-4-(3-metilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y *meta*-toluidina en 76% de rendimiento; Espectro NMR (CDCl₃) 2.03 (m, 2H), 2.34 (m, 7H), 2.40 (s, 3H), 2.82 (m, 2H), 3.92 (s, 3H), 4.58 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.27 (m, 1H), 7.53 (d, 1H), 7.56 (s, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Espectro de masa MH⁺ 379.

Ejemplo 2.7

4-(3-Fluoroanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 3-fluoroanilina en 41% de rendimiento; Espectro NMR (CDCl_3) 2.01 (m, 2H), 2.28 (m, 4H), 2.33 (s, 3H), 2.83 (m, 2H), 3.92 (s, 3H), 4.57 (m, 1H), 6.52 (d, 1H), 6.80 (m, 1H), 6.85 (d, 1H), 7.29 (m, 2H), 7.88 (m, 1H), 8.59 (s, 1H), 9.98 (s, 1H); Espectro de masa MH^+ 383.

Ejemplo 2.8

4-(Indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 5-aminoindol en 17% de rendimiento; Espectro NMR (CDCl_3) 2.06 (m, 2H), 2.22 - 2.38 (m, 7H), 2.77 (m, 2H), 3.91 (s, 3H), 4.61 (m, 1H), 6.50 (d, 1H), 6.36 (m, 1H), 7.22 (t, 1H), 7.38 (s, 2H), 7.96 (s, 1H), 8.25 (bs, 1H), 8.51 (s, 1H), 9.82 (s, 1H); Espectro de masa MH^+ 404.

Ejemplo 2.9

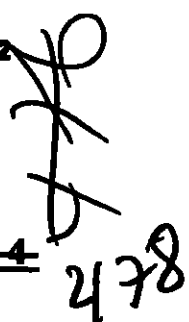
4-(3-Cloro-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 4-amino-2-clorofenol en 72% de rendimiento; Espectro NMR (DMSO-d_6) 1.9 (m, 2H), 2.1 (m, 2H), 2.2 (s, 3H), 2.3 (m, 2H), 2.6 (m, 2H), 3.9 (s, 3H), 4.8 (m, 1H) 6.8 (s, 1H), 7.0 (d, 3H), 7.3 (dd, 1H), 8.0 (d, 1H), 8.4 (s, 1H), 9.8 (s, 1H), 10.0 (bs, 1H); Espectro de masa MH^+ 415.

Ejemplo 2.10

4-(3-Metil-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 4-aminocresol en 84% de rendimiento; Espectro NMR (DMSO-d_6) 1.9 (m, 2H), 2.1 (m, 2H), 2.2 (s, 3H), 2.2 (s, 3H), 2.3 (m, 2H), 2.6 (m, 2H), 3.9 (s, 3H), 4.8 (m, 1H) 6.8 (s, 2H), 6.8 (d, 1H), 7.4 (dd, 1H), 7.4 (s, 1H), 8.4 (s, 1H), 9.2 (s, 1H), 9.7 (s, 1H), 10.0 (bs, 1H); Espectro de masa MH^+ 395.

**Ejemplo 3****Clorhidrato de 4-(3-metilbenzisotiazol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Una mezcla de 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) (0.42 g) y 5-amino-3-metilbenzisotiazol (Ejemplo de Referencia 27) (0.25 g) en IPA (10 ml) se calentaron reflujo durante 16 horas, luego se dejó enfriar a temperatura ambiente. Se precipitó un sólido de la mezcla y ésta se filtró, se lavó con IPA éter dietílico, y se secó *in vacuo* para proporcionar el compuesto del título como un sólido amarillo (0.4 g, 60%); Espectro de masa MH^+ 406.

El procedimiento descrito arriba se repitió usando la anilina apropiada y cloroquinazolina. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 3.1**Clorhidrato de 4-(3-etinil-4-(2-fluorobenciloxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) con 3-etinil-4-(2-fluorobenciloxi)anilina (Ejemplo de Referencia 42) en 67% de rendimiento; Espectro de masa MH^+ 514.

Ejemplo 3.2**Clorhidrato de 4-(3-etinil-4-(3-fluorobenciloxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) con 3-etinil-4-(3-fluorobenciloxi)anilina (Ejemplo de Referencia 42.1) en 60% de rendimiento; Espectro de masa MH^+ 514.

Ejemplo 3.3**Clorhidrato de 4-(3-fluoro-4-(1-metil-1*H*-imidazol-2-iltio)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) con 3-fluoro-4-(1-metil-

1*H*-imidazol-2-iltio)anilina (Ejempl de Referencia 26.3) en 54% de rendimiento; Espectro NMR (DMSO-d₆, 373K) 1.9 - 2.0 (m, 2H), 2.1 - 2.2 (m, 2H), 2.25 (s, 3H), 2.25 - 2.35 (m, 2H), 2.6 - 2.7 (m, 2H), 3.7 (s, 3H), 3.9 (s, 3H), 4.7 - 4.8 (m, 1H), 6.8 (d, 1H), 6.85 (d, 1H), 7.0 (s, 1H), 7.1 - 7.2 (t, 1H), 7.3 (s, 1H), 7.3 - 7.4 (dd, 1H), 8.0 - 8.1 (d, 1H), 8.5 (s, 1H), 10.0 (bs, 1H); Espectro de masa MH⁺ 495.

Ejemplo 4

4-(3-Bromoindazol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Di-*iso*-propiletilamina (94 µl) se agregó a una mezcla de 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) (75 mg) y 5-amino-3-bromoindazol (Ejemplo de Referencia 25) (115 mg) en IPA (12 ml). La suspensión resultante se calentó a reflujo durante 2 horas, luego se dejó enfriar a temperatura ambiente. Se precipitó un sólido de la mezcla y ésta se filtró, se lavó con IPA y éter dietílico, y se secó *in vacuo* para proporcionar el compuesto del título como un sólido blanco (114 mg, 93%); Espectro NMR (DMSO-d₆) 1.97 (m, 2H), 2.20 (m, 5H), 2.38 (m, 2H), 2.70 (m, 2H), 4.82 (m, 1H), 7.20 (d, 1H), 7.37 (d, 1H), 7.57-7.74 (m, 3H), 8.15 (s, 1H), 8.51 (s, 1H), 10.10 (s, 1H), 13.10 (bs, 1H); Espectro de masa MH⁺ 453, 455.

El procedimiento descrito arriba se repitió usando la 4-cloroquinazolina apropiada y anilina. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 4.1

4-(3-Cloroindazol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) y 5-amino-3-cloroindazol (Ejemplo de Referencia 25.1) en 85% de rendimiento; Espectro NMR (DMSO-d₆) 1.96 (m, 2H), 2.18 (m, 2H), 2.25 (s, 3H), 2.41 (m, 2H), 2.74 (m, 2H), 4.82 (m, 1H), 7.23 (d, 1H), 7.33 (d, 1H), 7.51 - 7.74 (m, 3H), 8.39 (s, 1H), 8.53(s, 1H), 10.21 (s, 1H), 13.29 (bs, 1H); Espectro de masa MH⁺ 409.

Ejemplo 4.2

F
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4-(3-Cloro-1-(2-Piridilmetil)indol-5-ilamin)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 5-amino-3-cloro-1-(2-piridilmetil)indole (Ejemplo de Referencia 26) en 10% de rendimiento; Espectro NMR (CDCl₃) 2.03 (m, 2H), 2.22 (m, 2H), 2.32 (s, 3H), 2.37 (m, 2H), 2.75 (m, 2H), 3.91 (s, 3H), 4.61 (m, 1H), 5.39 (s, 2H), 6.50 (d, 1H), 6.82 (m, 2H), 7.18 (m, 2H), 7.27 (d, 1H), 7.44 (dd, 1H), 7.56 (dt, 1H), 7.95 (d, 1H), 8.52 (s, 1H), 8.59 (d, 1H), 9.83 (s, 1H); Espectro de masa MH⁺ 529.

Ejemplo 4.3

4-(3-Cloro-1-(2-Piridilmetil)indazol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 5-amino-3-cloro-1-(2-piridilmetil)mdazol (Ejemplo de Referencia 26.1) en 9% de rendimiento; Espectro NMR (CDCl₃) 2.03 (m, 2H), 2.25 (m, 2H), 2.32 (s, 3H), 2.37 (m, 2H), 2.77 (m, 2H), 3.92 (s, 3H), 4.60 (m, 1H), 5.66 (s, 2H), 6.51 (d, 1H), 6.84 (d, 1H), 6.98 (d, 1H), 7.19 (dd, 2H), 7.39 (d, 1H), 7.58 (m, 2H), 8.13 (d, 1H), 8.55 (s, 1H), 8.58 (d, 1H), 9.88 (s, 1H); Espectro de masa MH⁺ 530.

Ejemplo 4.4

7-Metoxi-4-(3-metil-4-(2-piridilmetoxi)anilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y 3-metil-4-(2-piridilmetoxi)anilina (obtenida usando el método de Ejemplo 13 de WO 96/15118) en 18% de rendimiento; Espectro NMR (CDCl₃) 2.02 (m, 2H), 2.25 (m, 2H), 2.32 (s, 3H), 2.38 (s, 3H), 2.76 (m, 2H), 3.90 (s, 3H), 4.58 (m, 1H), 5.23 (s, 2H), 6.48 (d, 1H), 6.81 (d, 1H), 7.22 (dd, 1H), 7.44 (m, 2H), 7.56 (d, 1H), 7.23 (dt, 1H), 8.50 (s, 1H), 8.59 (d, 1H), 9.65 (s, 1H); Espectro de masa MH⁺ 486.

Ejempl 4.5**4-(3-Metilindol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) y 3-metilindol-5-ilamina (Ejemplo de Referencia 27.1) en 10% de rendimiento; Espectro NMR (DMSO-d₆); 2.2 - 2.4 (m, 5H), 2.8 (s, 3H), 3.2 - 3.7 (m, 6H), 5.1 (m, 1H), 7.2 (s, 1H), 7.3 - 7.6 (m, 4H), 7.8 - 8.0 (m, 2H), 8.8 (d, 1H); Espectro de masa MH⁺ 388.

Ejemplo 4.6**4-(3-Cloro-4-hidroxianilino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) y 3-cloro-4-hidroxianilina en 60% de rendimiento; Espectro NMR (DMSO-d₆) 1.9 (m, 2H), 2.1 (m, 5H), 2.3 (m, 2H), 2.6 (m, 2H), 4.8 (m, 1H), 7.0 (d, 1H), 7.2 (d, 1H), 7.3 (m, 2H), 7.7 (m, 1H), 8.0 (d, 1H), 8.4 (s, 1H), 10.0 (s, 1H); Espectro de masa MH⁺ 385.

Ejemplo 5**5-(1-Metilpiperidin-4-iloxi)-4-((1R)-1-Feniletilamino)quinazolina**

4-Cloro-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.1) (0.3 g), (*R*)- α -metilbencilamina (0.28 ml) y di-*iso*-propiletilamina (0.94 ml) se calentaron a reflujo en dioxano (20 ml) durante 3 horas. La solución se concentró *in vacuo* y el residuo se trituró con éter para proporcionar el compuesto del título como un sólido blanco (0.29 g, 74%); Espectro de masa MH⁺ 363.

El procedimiento descrito arriba se repitió usando la 4-cloroquinazolina apropiada y amina. Así se obtuvo el compuesto descrito a continuación:

Ejemplo 5.1**7-Metoxi-5-(1-metilpiperidin-4-iloxi)-4-((1R)-1-Feniletilamino)quinazolina**

Obtenida haciendo reaccionar 4-cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 16.2) y (*R*)- α -



metilbencilamina en 47% de rendimiento; Espectro de masa MH^+ 393.

Ejemplo 6

4-(3-Cloro-4-fluoroanilino)-7-(3-(R)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina

Di-*iso*-propiletilamina (0.18 ml) se agregó a 7-(3-(R)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 14) (50 mg) disuelta en 1, 2-dicloroetano anhidro (5 ml) y la solución resultante enfriada a 0°C. Se agregó $POCl_3$ (40 μ l) gota a gota y la reacción se calentó a 80°C durante 3 horas. La mezcla de reacción se concentró *in vacuo* para proporcionar un aceite anaranjado, el cual se usó sin purificación adicional. Se agregó 3-cloro-4-fluoroanilina (20 mg) a este aceite disuelto en IPA (300 μ l), seguida por di-*iso*-propiletilamina (11 μ l). La mezcla resultante se calentó a 80°C durante 12 horas para proporcionar un precipitado amarillo. La mezcla de reacción se enfrió a temperatura ambiente, el sólido se filtró, se lavó con IPA, luego éter dietílico y se secó *in vacuo* para proporcionar el compuesto del título como un sólido amarillo (25 mg, 37%); Espectro NMR (DMSO- d_6 , 373K) 2.3 - 2.6 (m, 3H), 2.8 (s, 3H), 2.9 (s, 6H), 3.0 - 3.6 (m, 7H), 3.8 (m, 1H), 3.9 (m, 2H), 4.1 (m, 1H), 5.3 (m, 1H), 6.5 (s, 1H), 6.7 (s, 1H), 7.5 (m, 1H), 7.7 (m, 1H), 8.1 (m, 1H), 8.6 (s, 1H), 10.1 (m, 1H); Espectro de masa MH^+ 499.

El procedimiento descrito arriba se repitió usando la 3,4-dihidroquinazolin-4-ona apropiada y anilina. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 6.1

4-(3-Cloro-4-fluoroanilino)-7-metoxi-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 7-metoxi-5-(tetrahydrofurano-3-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 14.1) y 3-cloro-4-fluoroanilina en 44% de rendimiento; Espectro NMR (DMSO- d_6) 2.20 (m, 1H), 2.35 (m, 1H), 3.84 (m, 3H), 3.95 (s, 3H), 4.19 (d, 1H), 5.56 (m, 1H), 7.01 (s, 2H), 7.53 (t, 1H), 7.63 (m, 1H), 8.11 (dd, 1H), 8.81 (s, 1H), 10.41

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(s, 1H); Espectro de masa MH^+ 390.

Ejemplo 6.2

4-(3-Cloro-4-fluoroanilino)-7-metoxi-5-(tetrahidropiran-4-iloxi)quinazolina

Obtenida haciendo reaccionar 7-metoxi-5-(tetrahidropiran-4-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 14.2) y 3-cloro-4-fluoroanilina en 56% de rendimiento; Espectro NMR (DMSO- d_6) 1.95 (m, 2H), 2.15 (m, 2H), 3.53 (m, 2H), 3.89 (m, 2H), 3.95 (s, 3H), 5.08 (m, 1H), 7.00 (d, 1H), 7.09 (d, 1H), 7.59 (m, 2H), 8.06 (dd, 1H), 8.81 (s, 1H), 10.46 (s, 1H); Espectro de masa MH^+ 404.

Ejemplo 6.3

5-(1-*tert*-Butoxicarbonilpiperidin-4-iloxi)-4-(3-cloro-4-fluoroanilino)-7-metoxiquinazolina

Obtenida haciendo reaccionar 5-(1-*tert*-butoxicarbonilpiperidin-4-iloxi)-7-metoxi-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 15) y 3-cloro-4-fluoroanilina en 54% de rendimiento; Espectro NMR (CDCl₃) 1.48 (s, 9H), 1.86 (m, 2 H), 2.24 (m, 2H), 3.20 (m, 2H), 3.92 (s, 3H), 4.00 (m, 2H), 4.69 (m, 1H), 6.53 (d, 1H), 6.87 (d, 1H), 7.14 (t, 1H), 7.39 (m, 1H), 8.02 (dd, 1H), 8.57 (s, 1H), 9.70 (s, 1H); Espectro de masa MH^+ 503.

Ejemplo 6.4

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 14) y 3-cloro-4-(3-fluorobenciloxi)anilina (Ejemplo de Referencia 28) en 61% de rendimiento; Espectro de masa M^+ 605.

Ejemplo 6.5

4-(3-Cloroanilino)-7-(3-(*S*)-dimetilaminopirrolidin-1-il)-5-(tetrahidropiran-4-iloxi)quinazolina

Obtenida haciendo reaccionar 7-(3-(*S*)-dimetilaminopirrolidin-1-il)-5-(tetrahidropiran-4-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 11.1) y 3-cloroanilina en 73% de rendimiento; Espectro de

masa M^+ 468.

Ejemplo 7

4-(3-Cloro-4-fluoroanilino)-7-metoxi-5-(tetrahidrotiofen-3-iloxi)quinazolina

4-(3-Cloro-4-fluoroanilino)-5-hidroxi-7-metoxiquinazolina (Ejemplo de Referencia 10) (200 mg), trifenilfosfina (247 mg) y 3-hidroxitetrahidrotiofene (98 mg) se disolvieron en DCM anhidro (30 ml) bajo una atmósfera de nitrógeno y se enfriaron a 0°C. Se agregó azodicarboxilato di-*tert*-butílico (217 mg) en DCM (1 ml) gota a gota a la reacción, manteniendo la temperatura interna < 5 °C. La reacción se dejó calentar a temperatura ambiente durante 1 hora y luego se agitó a temperatura ambiente durante 1 hora. La reacción se concentró *in vacuo* y el residuo se purificó por cromatografía usando 1-5% metanol en DCM como eluyente para proporcionar el compuesto del título como un sólido blanco (24 mg, 10%); Espectro de masa MH^+ 404.

El procedimiento descrito arriba se repitió usando la 5-hidroxiquinazolina apropiada y alcohol. Así se obtuvo el compuesto descrito a continuación:

Ejemplo 7.1

4-(3-Cloro-4-fluoroanilino)-7-metoxi-5-(1-iso-propilazetidín-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-5-hidroxi-7-metoxiquinazolina (Ejemplo de Referencia 10) y 3-hidroxi-1-iso-propilazetidina (obtenida como se describe en *J. Org. Chem.*, 1967, 32, 2972-75) en 13% de rendimiento; Espectro de masa MH^+ 417.

Ejemplo 8

4-(3-Cloro-4-fluoroanilino)-5-(tetrahidrotiopiran-4-iloxi)quinazolina

Hidruro de sodio (180 mg, 60% dispersión en aceite) se agregó en porciones a 4-hidroxi-tetrahidrotiopirano (Ejemplo de Referencia 36) (320 mg) y clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) (300 mg) en DMF (5 ml) a temperatura ambiente. Al disminuir la espumación, la reacción se calentó a 120°C

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durante 2 horas para proporcionar una solución negra. La mezcla de reacción se concentró *in vacuo* y el residuo se purificó por cromatografía usando 1-5% metanol en DCM como eluyente para proporcionar a aceite incoloro, el cual se cristalizó al reposar. Se agregó éter dietílico y se filtró el producto para proporcionar el compuesto del título como un sólido blanco (235 mg, 65%); Espectro NMR (DMSO-d₆) 1.82 (m, 1H), 1.98 (m, 3H), 2.53 - 2.71 (m, 2H), 2.98 - 3.01 (m, 1H), 3.15 (m, 1H), 5.03 (m, 1H), 7.22 (d, 1H), 7.35 (d, 1H), 7.43 (t, 1H), 7.71 (m, 2H), 8.22 (dd, 1H), 8.53 (s, 1H), 10.32 (s, 1H); Espectro de masa MH⁺ 390.

El procedimiento descrito arriba se repitió usando el alcohol apropiado y 5-fluoroquinazolina. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 8.1

4-(3-Cloro-4-fluoroanilino)-5-(tetrahidrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y 3-hidroxitetrahidrofurano en 72% de rendimiento; Espectro de masa MH⁺ 360.

Ejemplo 8.2

4-(3-Cloro-4-fluoroanilino)-5-(tetrahidropiran-4-iloxi)quinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y 4-hidroxi-tetrahidropirano en 45% de rendimiento; Espectro de masa MH⁺ 374.

Ejemplo 8.3

4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxiquinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y ciclopentanol en 40% de rendimiento; Espectro de masa MH⁺ 358.

Ejemplo 8.4

4-(3-Cloro-4-fluoroanilino)-5-(1-metilpirrolidin-3-iloxi)quinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-

fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y 3-hidroxi-1-metilpirrolidina en 34% de rendimiento; Espectro de masa MH^+ 371.

Ejemplo 8.5

4-(3-Cloro-4-fluoroanilino)-5-(1-iso-propilazetidin-3-iloxi)quinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y 3-hidroxi-1-iso-propilazetidina en 54% de rendimiento; Espectro de masa MH^+ 387.

Ejemplo 8.6

4-(3-Cloro-4-fluoroanilino)-5-(tetrahidrotiofen-3-iloxi)quinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y 3-hidroxitetrahidrotiofeno en 66% de rendimiento; Espectro de masa MH^+ 376.

Ejemplo 8.7

4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-3-iloxi)quinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y 3-hidroxi-1-metilpiperidina en 51% de rendimiento; Espectro NMR (DMSO- d_6) 1.25 (t, 1H), 1.47-1.72 (m, 3H), 2.02 (m, 2H), 2.30 (s, 3H), 2.81 (m, 1H), 3.14 (m, 1H), 5.08 (m, 1H), 7.19 (d, 1H), 7.33 (d, 1H), 7.44 (t, 1H), 7.73 (t, 1H), 8.00 (m, 1H), 8.19 (dd, 1H), 8.56 (s, 1H), 10.78 (bs, 1H); Espectro de masa MH^+ 387.

Ejemplo 8.8

4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y 4-hidroxi-1-metilpiperidina en 21% de rendimiento; Espectro de masa M^+ 387.

Ejemplo 8.9

5-(1-tert-Butoxicarbonilazetidin-3-iloxi)-4-(3-cloro-4-

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fluoroanilino)quinazolina

Obtenida haciendo reaccionar clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina (Ejemplo de Referencia 18) y 1-*tert*-butoxicarbonilazetidin-3-ol (obtenido como se describe en *J. Med. Chem.*, (2001), 44(1), 94-104) en 16% de rendimiento; Espectro NMR (DMSO- d_6); 1.4 (s, 9H), 4.1 (m, 2H), 4.4 (m, 2H), 5.2 (m, 1H), 6.8 (d, 1H), 7.4 (m, 2H), 7.7 (m, 2H), 8.2 (d, 1H), 8.6 (s, 1H). 9.8 (s, 1H); Espectro de masa MH^+ 445

Ejemplo 9**4-(3-Cloro-4-fluoroanilino)-5-(1,1-dioxo-tetrahidrotiofen-3-iloxi)quinazolina y 4-(3-Cloro-4-fluoroanilino)-5-(1-oxo-tetrahidrotiofen-3-iloxi)quinazolina**

m-CPBA (240 mg) se agregó a 4-(3-cloro-4-fluoroanilino)-5-(tetrahidrotiofen-3-iloxi)quinazolina (ejemplo 8.6) (192 mg) en DCM (10 ml) a 0°C. La reacción se agitó a esta temperatura durante 30 minutos, luego se concentró y el residuo se purificó por cromatografía usando 1-8% metanol en DCM como eluyente para proporcionar en primer término 4-(3-cloro-4-fluoroanilino)-5-(1,1-dioxo-tetrahidrotiofen-3-iloxi)quinazolina como un sólido beige (64.8 mg, 62%); Espectro de masa $M-H^+$ 408; seguido por 4-(3-cloro-4-fluoroanilino)-5-(1-oxotetrahidrotiofen-3-iloxi)quinazolina como un sólido beige (33.4 mg, 33%); Espectro de masa $M-H^+$ 392.

El procedimiento descrito arriba se repitió usando el sulfuro apropiado. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 9.1**4-(3-Cloro-4-fluoroanilino)-5-((tetrahidrotiopiran-1,1-dióxido)-4-iloxi)quinazolina y 4-(3-Cloro-4-fluoroanilino)-5-((tetrahidrotiopiran-1-óxido)-4-iloxi)quinazolina**

Obtenidas de 4-(3-cloro-4-fluoroanilino)-5-(tetrahidrotiopiran-4-iloxi)quinazolina (ejemplo 8) en 94% de rendimiento; Espectro de masa $M-H^+$ 422; y 6% de rendimiento; Espectro de masa $M-H^+$ 406, respectivamente.

Ejempl 10

4-(3-cloro-4-(3-fluorobencil xi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Cloruro de 3-fluorobencilo (80 mg) se agregó a una mezcla de 4-(3-cloro-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.9) (207 mg) y carbonato de potasio (700 mg) en DMF (15 ml). La mezcla se agitó vigorosamente a temperatura ambiente durante 72 horas, luego se concentró *in vacuo*. El aceite resultante se dividió en porciones entre agua y acetato de etilo. Seguidamente se secaron los extractos orgánicos combinados (sulfato de sodio) y se concentraron para proporcionar el producto crudo, el cual se purificó por cromatografía usando 0-10% metanol en DCM como eluyente para proporcionar el compuesto del título como un sólido blanco (110 mg, 42%); Espectro NMR (CDCl₃) 2.0 (m, 2H), 2.3 (m, 4H), 2.3 (s, 3H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.1 (s, 2H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (t, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 523.

Ejemplo 10.1

4-(3-Cloro-4-(5-metilisoxazol-3-ilmetoxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.9) con 3-clorometil-5-metilisoxazol en 60% de rendimiento; Espectro NMR (CDCl₃) 2.0 (m, 2H), 2.3 (m, 4H), 2.3 (s, 3H), 2.4 (s, 3H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.2 (s, 2H), 6.2 (s, 1H), 6.5 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H), 7.4 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 510.

Ejemplo 10.2

4-(3-Cloro-4-(tiazol-4-ilmetoxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.9) con 4-clorometiltiazol en 60% de rendimiento; Espectro NMR (CDCl₃) 2.0 (m, 2H), 2.3 (m, 7H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.4 (s, 2H), 6.5 (d,

1H), 6.8 (d, 1H), 7.0 (d, 1H), 7.5 (m, 2H), 7.9 (d, 1H), 8.5 (s, 1H), 8.8 (d, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 512.

Ejemplo 10.3

4-(3-Cloro-4-(4-piridilmetoxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.9) con cloruro de 4-picolilo en 45% de rendimiento; Espectro NMR ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 7H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.2 (s, 2H), 6.5 (s, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.4 (d, 2H), 7.5 (d, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 8.6 (d, 2H), 9.8 (s, 1H); Espectro de masa MH^+ 506.

Ejemplo 10.4

4-(3-Cloro-4-benciloxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.9) con cloruro de bencilo en 47% de rendimiento; Espectro NMR ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 7H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H), 7.4 (m, 6H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 505.

Ejemplo 10.5

4-(3-Cloro-4-(2-cianobenciloxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.9) con 2-clorometilbenzonitrilo en 63% de rendimiento; Espectro NMR ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 7H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.3 (s, 2H), 6.5 (s, 1H), 6.8 (s, 1H), 7.0 (d, 1H), 7.4 (m, 2H), 7.7 (m, 2H), 7.8 (d, 1H), 8.0 (s, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Espectro de masa MH^+ 530.

Ejemplo 10.6

4-(4-Benciloxi-3-metilanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-metil-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.10) y cloruro de bencilo en 63% de rendimiento; Espectro NMR (CDCl_3) 2.0 (m, 2H), 2.2 (m, 2H), 2.3 (s, 3H), 2.3 (s, 3H), 2.4 (m, 2H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.3 - 7.5 (m, 7H), 8.5 (s, 1H), 9.6 (s, 1H); Espectro de masa MH^+ 485.

Ejemplo 10.7

4-(4-(2-Fluorobenciloxi)-3-metilanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-metil-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.9) con 2-fluorocloruro de bencilo en 72% de rendimiento; Espectro NMR (CDCl_3) 2.0 (m, 2H), 2.2 - 2.4 (m, 10H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.2 (s, 2H), 6.5 (s, 1H), 6.8 (s, 1H), 6.9 (d, 1H), 7.1 (m, 2H), 7.3 (m, 1H), 7.5 (m, 3H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 503.

Ejemplo 10.8

4-(4-(2,6-Difluorobenciloxi)-3-metilanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-metil-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.10) con 2,6-difluorocloruro de bencilo en 81% de rendimiento; Espectro NMR (CDCl_3) 2.0 (m, 2H), 2.2 (m, 5H), 2.3 (m, 5H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (t, 2H), 7.0 (d, 1H), 7.3 (m, 1H), 7.4 (m, 1H), 7.5 (dd, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 521.

Ejemplo 10.9

4-(4-(2-Cianobenciloxi)-3-metilanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-metil-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.10) con 2-clorometil benzonitrilo en 83% de rendimiento; Espectro NMR (CDCl_3) 2.0 (m, 2H), 2.2 (m, 2H), 2.3 (s, 3H), 2.3 (s, 3H), 2.4 (m, 2H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.3 (s, 2H), 6.5 (s, 1H), 6.8 (s, 1H), 6.9 (m, 1H), 7.4 (m, 3H),

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490

7.6 (t, 1H), 7.7 (m, 2H), 8.5 (s, 1H), 9.7 (s, 1H): Espectro de masa MH^+ 510.

Ejemplo 10.10

4-(3-Metil-4-(5-metilisoxazol-3-ilmetoxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-metil-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.10) con 3-clorometil-5-metilisoxazol en 81% de rendimiento; Espectro NMR ($CDCl_3$) 2.0 (m, 2H), 2.2 - 2.4 (m, 4H), 2.3 (s, 3H), 2.3 (s, 3H), 2.4 (s, 3H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.1 (s, 2H), 6.1 (s, 1H), 6.5 (s, 1H), 6.8 (s, 1H), 6.9 (m, 1H), 7.5 (m, 2H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 490.

Ejemplo 10.11

4-(3-Metil-4-(tiazol-4-ilmetoxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-metil-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.10) con 4-clorometiltiazol en 31% de rendimiento; Espectro NMR ($CDCl_3$) 2.0 (m, 2H), 2.2 - 2.4 (m, 10H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.3 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.4 - 7.5 (m, 3H), 8.5 (s, 1H), 8.8 (d, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 492.

Ejemplo 10.12

4-(4-(3-Fluorobenciloxi)-3-metilanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-metil-4-hidroxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.10) con 3-fluorocloruro de bencilo en 57% de rendimiento; Espectro NMR ($CDCl_3$) 2.0 (m, 2H), 2.2 - 2.4 (m, 10H), 2.8 (m, 2H), 3.9 (s, 3H), 4.6 (m, 1H) 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.4 - 7.5 (m, 2H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 503.

Ejemplo 11

4-(3-Cloro-4-fluoroanilino)-7-(2-metoxietoxi)-5-(tetrahidropiran-4-iloxi)quinazolina

Se agregaron carbonato de potasio (0.14 g) y 2-bromoetil metil éter (73 μ l) a una suspensión de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(tetrahidropiran-4-iloxi)quinazolina trifluoroacetato (Ejemplo de Referencia 20) en DMF (3 ml). La mezcla se agitó a temperatura ambiente durante 20 horas, a continuación se agregó más 2-bromoetil metil éter (97 μ l) y la mezcla se agitó a temperatura ambiente durante 20 horas más. La mezcla se concentró entonces *in vacuo*, el residuo se enfrió y se agregó agua fría. El sólido resultante se filtró, se lavó con agua fría y se secó *in vacuo* para proporcionar el compuesto del título como un sólido beige (0.09g, 78%); Espectro NMR (DMSO-d₆) 1.85 (m, 2H), 2.17 (m, 2H), 3.31 (s, 3H), 3.54 (t, 2H), 3.70 (m, 2H), 3.89 (m, 2H), 4.23 (m, 2H), 4.98 (m, 1H), 6.80 (d, 2H), 6.87 (d, 1H), 7.41 (t, 1H), 7.51-7.58 (m, 1H), 8.28 (m, 1H), 8.47 (s, 1H), 9.89 (s, 1H); Espectro de masa MH⁺ 446.

El procedimiento descrito arriba se repitió usando la 7-hidroxiquinazolina apropiada y halogenuro de alquilo o tosilato. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 11.1

4-(3-Bromoanilino)-7-(2-metoxietoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar trifluoroacetato de 4-(3-bromoanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 20.1) y 2-bromoetil metil éter en 43% de rendimiento; Espectro NMR (DMSO-d₆) 2.2 (m, 2H), 2.4 - 2.6 (m, 7H), 2.7 (m, 2H), 3.3 (s, 3H), 3.7 (m, 2H), 4.2 (m, 2H), 5.0 (m, 1H), 6.9 (dd, 2H), 7.3 (m, 2H) 7.6 (m, 1H), 8.3 (s, 1H), 8.5 (s, 1H); Espectro de masa MH⁺ 489.

Ejemplo 11.2

4-(3-Cloro-4-fluoroanilino)-7-(2-metoxietoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(tetrahidrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 20.2) y 2-bromoetil metil éter en 79% de rendimiento; Espectro NMR (DMSO-d₆) 2.16 (m, 1H), 2.32 (m, 1H), 3.32 (s, 3H), 3.71

(m, 2H), 3.78-3.97 (m, 3H), 4.21 (m, 3H), 5.47 (m, 1H), 6.82 (s, 2H), 7.42 (t, 1H), 7.60 (m, 1H), 8.28 (m, 1H), 8.49 (s, 1H), 9.91 (s, 1H); Espectro de masa MH^+ 434.

Ejemplo 11.3

4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-(2-metoxietoxi)quinazolina

Obtenida haciendo reaccionar trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-5-ciclopentiloxi-7-hidroxiquinazolina (Ejemplo de Referencia 20.3) y 2-bromoetil metil éter en 96 % de rendimiento; Espectro NMR (DMSO-d6) 1.72 (m, 4H), 2.00 (m, 4H), 3.31 (s, 3H), 3.70 (m, 2H), 4.23 (m, 2H), 5.19 (m, 1H), 6.70 (d, 1H), 6.79 (d, 1H), 7.45 (m, 2H), 8.25 (m, 1H), 8.46 (s, 1H), 9.88 (s, 1H); Espectro de masa MH^+ 432.

Ejemplo 11.4

7-(2-Metoxietoxi)-4-(3-metilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar trifluoroacetato de 7-hidroxi-4-(3-metilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 20.5) y 2-bromoetil metil éter en 36% de rendimiento; Espectro NMR (DMSO-d6) 1.8 (m, 2H), 2.1 (m, 5H), 2.3 (m, 5H), 2.6 (m, 2H), 3.3 (s, 3H), 3.7 (m, 2H), 4.2 (m, 2H), 4.8 (m, 1H), 6.8 (m, 2H), 7.0 (m, 1H), 7.2 (m, 1H), 7.5 (m, 1H), 7.6 (s, 1H), 8.4 (s, 1H), 9.9 (s, 1H); Espectro de masa MH^+ 423.

Ejemplo 11.5

4-(3-Cloro-4-fluoroanilino)-7-(2-metoxietoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 20.4) y 2-bromoetil metil éter en 53% de rendimiento; Espectro NMR (DMSO-d6) 1.8 (m, 2H), 2.1 (m, 5H), 2.3 (m, 2H), 2.6 (m, 2H), 3.3 (s, 3H), 3.7 (m, 2H), 4.2 (m, 2H), 4.8 (m, 1H), 6.8 (m, 2H), 7.4 (t, 1H), 7.6 (m, 1H), 8.2 (m, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa $M-H^+$ 459.

493

Ejemplo 11.6**4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-((1-tert-butoxicarbonilpiperidin-4-il)metoxi)quinazolina**

Obtenida haciendo reaccionar *N*-tert-butoxicarbonil-4-tosiloximetilpiperidina (Ejemplo de Referencia 41) y 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-hidroxiquinazolina (Ejemplo de Referencia 20.8) en 65% de rendimiento; Espectro NMR (CDCl₃) 1.3 (m, 2H), 1.5 (s, 9H), 1.8 (m, 2H), 2.0 (m, 3H), 2.2 - 2.4 (m, 7H), 2.8 (m, 4H), 3.9 (d, 2H), 4.2 (m, 2H), 4.6 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H): Espectro de masa MH⁺ 706.

Ejemplo 11.7**4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-metoxietoxi)quinazolina**

Obtenida haciendo reaccionar bromuro de 2-metoxietilo y 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-hidroxiquinazolina (Ejemplo de Referencia 20.8) en 64% de rendimiento como un sólido blanco; Espectro NMR (CDCl₃) 2.0 (m, 2H), 2.2 - 2.3 (m, 7H), 2.8 (m, 2H), 3.5 (s, 3H), 3.8 (m, 2H), 4.2 (m, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.6 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H): Espectro de masa MH⁺ 567.

Ejemplo 11.8**4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-((1-tert-butoxicarbonilpiperidin-4-il)metoxi)quinazolina**

Obtenida haciendo reaccionar *N*-tert-butoxicarbonil-4-tosiloximetilpiperidina (Ejemplo de Referencia 41) y 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-hidroxiquinazolina (Ejemplo de Referencia 20.9) en 69% de rendimiento; Espectro NMR (CDCl₃) 1.3 (m, 2H), 1.5 (s, 9H), 1.8 (m, 2H), 2.0 (m, 3H), 2.2 - 2.3 (m, 2H), 2.8 (m, 2H), 3.6 (m, 2H), 3.9 (d, 2H), 4.0 (dt, 2H), 4.2 (m, 2H), 4.8 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2

(m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 693.

Ejemplo 11.9

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(2-metoxietoxi)-5-(3-tetrahidrofuranoiloxi)quinazolina

Obtenida haciendo reaccionar 2-bromoetil metil éter con 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-hidroxi-5-(3-tetrahidrofuranoiloxi)quinazolina (125 mg) (Ejemplo de Referencia 20.10) en 35% de rendimiento; Espectro de masa MH^+ 540.

Ejemplo 12

4-(3-Cloroanilino)-7-(1-metilpiperidin-4-ilmetoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina

7-(1-*tert*-Butoxicarbonilpiperidin-4-ilmetoxi)-4-(3-cloroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 22.1) (50 mg) se calentó a 80°C en ácido fórmico (2 ml) y formaldehído acuoso (1 ml) durante 15 horas. El solvente se retiró *in vacuo* para proporcionar un sólido rosado. Se agregó 7N amoníaco en metanol se agregó y el solvente se retiró *in vacuo*. Se agregó agua se agregó y el sólido así obtenido se filtró y se secó para proporcionar el compuesto del título como un sólido beige; (30 mg, 71%); Espectro NMR (DMSO- d_6) 1.3 (m, 2H), 1.6 - 2.0 (m, 7H), 2.1 (m, 8H), 2.3 (m, 2H), 2.6 (m, 2H), 2.8 (m, 2H), 4.0 (d, 2H), 4.8 (m, 1H), 6.8 (d, 2H), 7.1 (d, 1H), 7.4 (t, 1H), 7.5 (d, 1H), 8.2 (s, 1H), 8.5 (s, 1H), 10.0 (s, 1H); Espectro de masa MH^+ 496.

El procedimiento descrito arriba se repitió usando la 1-*tert*-butoxicarbonil amina apropiada. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 12.1

4-(3-Cloro-4-fluoroanilino)-7-(1-metilpiperidin-4-ilmetoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida de 7-(1-*tert*-butoxicarbonilpiperidin-4-ilmetoxi)-4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 22) en 35% de rendimiento; Espectro NMR (DMSO- d_6) 1.3

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(m, 2H), 1.7 (m, 4H), 1.9 (m, 4H), 2.1 (m, 7H), 2.3 (m, 2H), 2.6 (m, 2H), 2.8 (m, 2H), 4.0 (d, 2H), 4.8 (m, 1H), 6.8 (d, 2H), 7.4 (t, 1H), 7.6 (m, 1H), 8.2 (dd, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH^+ 514.

Ejemplo 12.2

4-(3-Cloro-4-fluoroanilino)-5-(1-metilazetidin-3-iloxi)quinazolina

Obtenida de 5-(1-*tert*-butiloxicarbonilazetidin-3-iloxi)-4-(3-cloro-4-fluoroanilino)quinazolina (ejemplo 8.9) en 18% de rendimiento; Espectro NMR (DMSO- d_6) 2.3 (s, 3H), 3.3 (m, 2H), 3.8 (m, 2H), 5.1 (m, 1H), 6.9 (d, 1H), 7.4 (m, 2H), 7.7 (m, 2H), 8.3 (d, 1H), 8.6 (s, 1H); Espectro de masa MH^+ 359.

Ejemplo 12.3

4-(3-Cloro-4-fluoroanilino)-7-(1-metilpiperidin-4-ilmetoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida de 4-(3-cloro-4-fluoroanilino)-7-(1-*tert*-butoxicarbonilpiperidin-4-ilmetoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 22.2) en 94% de rendimiento; Espectro NMR (DMSO- d_6) 1.36 (m, 2H), 1.75 (m, 2H), 1.90 (m, 2H), 2.18 (s, 3H), 2.22 - 2.40 (m, 1H), 2.50 (m, 2H), 2.79 (m, 2H), 3.78 - 3.98 (m, 5H), 4.18 (d, 1H), 5.45 (m, 1H), 6.80 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.40 (m, 1H), 8.52 (s, 1H), 9.87 (s, 1H); Espectro de masa MH^+ 488.

Ejemplo 13

4-(3-Cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina

Ácido trifluoroacético (20 ml) se agregó a una muestra sólida de 5-(1-*tert*-butoxicarbonilpiperidin-4-iloxi)-4-(3-cloro-4-fluoroanilino)-7-metoxiquinazolina (ejemplo 6.3) (200 mg), luego se agitó a temperatura ambiente durante 10 minutos. El exceso de ácido trifluoroacético se retiró *in vacuo*, a continuación se agregó cuidadosamente carbonato hidrogenado de sodio acuoso saturado (efervescencia). Seguidamente se extrajo el producto en DCM, se secó sobre sulfato de sodio y se concentró *in vacuo* para proporcionar el material crudo, el cual se purificó por cromatografía usando 0-10% metanol en DCM como eluyente, para proporcionar el compuesto del título como un sólido blanco (130 mg, 81%): Espectro NMR

(DMSO-d₆) 1.84 (m, 2H), 2.24 (m, 2H), 2.83 (m, 2H), 2.40 (m, 2H), 3.12 (m, 2H), 3.35 (bs, 1H), 3.92 (s, 3H), 4.91 (m, 1H), 6.85 (d, 1H), 6.87 (d, 1H), 7.47 (t, 1H), 7.59 (m, 1H), 8.28 (dd, 1H), 8.52 (s, 1H), 9.94 (s, 1H); Espectro de masa MH⁺ 403.

El procedimiento descrito arriba se repitió usando la amina apropiada protegida con *tert*-butoxicarbonilo. Así se obtuvo el compuesto descrito a continuación:

Ejemplo 13.1

4-(3-Cloro-4-fluoroanilino)-7-(piperidin-4-ilmetoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina

Obtenida de 4-(3-cloro-4-fluoroanilino)-7-(1-*tert*-butoxicarbonilpiperidin-4-ilmetoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 22.2) en 73% de rendimiento; Espectro NMR (DMSO-d₆) 1.48 (m, 2H), 1.95 (m, 2H), 2.02 - 2.20 (m, 2H), 2.30 (m, 1H), 2.92 (m, 2H), 3.30 (m, 2H), 3.78 - 3.98 (m, 3H), 4.03 (d, 2H), 4.19 (d, 1H), 5.45 (m, 1H), 6.80 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.43 (m, 1H), 8.52 (s, 1H), 9.87 (s, 1H); Espectro de masa MH⁺ 474.

Ejemplo 13.2

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(piperidin-4-ilmetoxi)quinazolina

Obtenida de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-((1-*tert*-butoxicarbonilpiperidin-4-il)metoxi)quinazolina (ejemplo 11.6) en 78% de rendimiento; Espectro NMR (CDCl₃) 1.3 (m, 2H), 1.8 (m, 2H), 2.0 (m, 3H), 2.2 - 2.4 (m, 7H), 2.6 - 2.8 (m, 4H), 3.2 (m, 2H), 3.9 (d, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 606.

Ejemplo 13.3

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(piperidin-4-ilmetoxi)quinazolina

Obtenida de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-((1-*tert*-butoxicarbonilpiperidin-4-il)

metoxi)quinazolina (ejemplo 11.8) en 72% de rendimiento; Espectro NMR (CDCl_3) 1.3 (m, 2H), 1.8 (m, 2H), 2.0 (m, 3H), 2.3 (m, 2H), 2.7 (m, 2H), 3.1 (m, 2H), 3.6 (m, 2H), 3.9 (d, 2H), 4.1 (m, 2H), 4.7 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 593.

Ejemplo 14

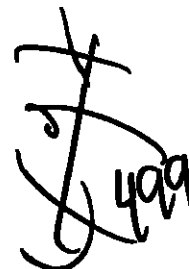
5-(N-Acetilpiperidin-4-iloxi)-4-(3-cloro-4-fluoroanilino)-7-metoxiquinazolina

Cloruro de acetilo (0.18 ml) se agregó a una solución de 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (90 mg) (ejemplo 13) y 4-(dimetilamino)piridina (aproximadamente 1 mg) en piridina (20 ml). La mezcla se agitó luego a temperatura ambiente durante 1 hora, y se concentró *in vacuo*. El residuo se disolvió en DCM, y se lavó con carbonato hidrogenado de sodio acuoso saturado, sulfato de cobre (II) acuoso, luego agua. El secamiento sobre sulfato de sodio, seguido por concentración *in vacuo* produjo un aceite viscoso amarillo. La purificación por cromatografía, usando 0-2% metanol en DCM como eluyente, produjo el compuesto del título como una espuma amarilla, la cual se trituró bajo acetonitrilo frío para proporcionar el producto como un sólido blanco (30 mg, 29%); Espectro NMR (CDCl_3) 1.88 (m, 2H), 2.15 (s, 3H), 2.29 (m, 2H), 3.26 (m, 1H), 3.39 (m, 1H), 3.84 (m, 1H), 3.93 (s, 3H), 4.32 (m, 1H), 4.76 (m, 1H), 6.53 (d, 1H), 6.87 (d, 1H), 7.14 (t, 1H), 7.36 (m, 1H), 8.01 (dd, 1H), 8.57 (s, 1H), 9.63 (s, 1H); Espectro de masa MH^+ 445.

Ejemplo 15

4-(3-Cloro-4-fluoroanilino)-7-metoxi-5-(1-propilpiperidin-4-iloxi)quinazolina

Triacetoxiborohidruro de sodio (63 mg) se agregó a una solución agitada de 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (ejemplo 13) (100 mg), propionaldehído (0.18 ml) y ácido acético (0.5 ml) en 1, 2-dicloroetano (10 ml) a temperatura ambiente. Después de 15 minutos, la mezcla de reacción se diluyó con agua, y se



agregó carbonato de potasio sólido (exceso). La mezcla resultante se extrajo en DCM, se secó sobre sulfato de sodio, y se concentró *in vacuo* para proporcionar el material crudo como un aceite incoloro, el cual se solidificó con la adición de éter dietílico. La trituración de este sólido con metanol frío produjo el compuesto del título como un polvo blanco (110 mg, 100%); Espectro NMR (CDCl_3) 0.92 (t, 3H), 1.53 (m, 2H), 1.98 (m, 2H), 2.25 (m, 6H), 2.87 (m, 2H), 3.91 (s, 3H), 4.57 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.46 (m, 1H), 8.00 (dd, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Espectro de masa MH^+ 445.

El procedimiento descrito arriba se repitió usando la amina apropiada y aldehído. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 15.1

5-(1-Etilpiperidin-4-iloxi)-4-(3-cloro-4-fluoroanilino)-7-metoxiquinazolina

Obtenida de 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (ejemplo 13) y acetaldehído en 80% de rendimiento; Espectro NMR (CDCl_3) 1.11 (t, 3H), 2.00 (m, 2H), 2.31 (m, 4H), 2.46 (q, 2H), 2.88 (m, 2H), 3.91 (s, 3H), 4.58 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.46 (m, 1H), 8.00 (dd, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Espectro de masa MH^+ 431.

Ejemplo 15.2

4-(3-Cloro-4-fluoroanilino)-7-metoxi-5-(1-(2-metoxietil)piperidin-4-iloxi)quinazolina

Obtenida de 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (ejemplo 13) y 2-metoxiacetaldehído en 68% de rendimiento; Espectro NMR (CDCl_3) 2.03 (m, 2H), 2.25 (m, 2H), 2.39 (m, 2H), 2.62 (t, 2H), 2.93 (m, 2H), 3.36 (s, 3H), 3.52 (t, 2H), 3.91 (s, 3H), 4.57 (m, 1H), 6.50 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.45 (m, 1H), 8.01 (dd, 1H), 8.56 (s, 1H), 9.83 (s, 1H); Espectro de masa MH^+ 461.

Ejemplo 16

4-(3-Cloro-4-fluoroanilino)-5-(1-(2-propinil)piperidin-4-iloxi)-7-metoxiquinazolina

Bromuro de propargilo (80% p/p en tolueno, 60 mg) se agregó a una mezcla de 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (ejemplo 13) (100 mg) y carbonato de potasio (343 mg) en DMF (15 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas, luego se vertió en agua. El fino precipitado blanco resultante se recuperó por filtración, luego se purificó por LC-MS preparativa, para proporcionar el compuesto del título como un sólido blanco (56 mg, 51%); Espectro NMR (CDCl_3) 2.03 (m, 2H), 2.19 (t, 1H), 2.30 (m, 2H), 2.56 (m, 2H), 2.91 (m, 2H), 3.39 (d, 2H), 3.92 (s, 3H), 4.61 (m, 1H), 6.52 (d, 1H), 6.85 (d, 1H), 7.13 (t, 1H), 7.47 (m, 1H), 8.01 (dd, 1H), 8.56 (s, 1H), 9.80 (s, 1H); Espectro de masa MH^+ 441.

El procedimiento descrito arriba se repitió usando el halogenuro de alquilo o alquenilo apropiado y amina. Así se obtuvo el compuesto descrito a continuación:

Ejemplo 16.1

5-(1-Alilpiperidiu-4-iloxi)-4-(3-cloro-4-fluoroanilino)-7-metoxiquinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (ejemplo 13) con bromuro de alilo en 45% de rendimiento; Espectro NMR (CDCl_3) 1.99 (m, 2H), 2.31 (m, 4H), 2.89 (m, 2H), 3.05 (d, 2H), 3.91 (s, 3H), 4.57 (m, 1H), 5.19 (m, 2H), 5.87 (m, 1H), 6.51 (d, 1H), 6.84 (d, 1H), 7.12 (t, 1H), 7.47 (m, 1H), 7.99 (dd, 1H), 8.56 (s, 1H), 9.82 (s, 1H); Espectro de masa MH^+ 443.

Ejemplo 17

Metil 2-(4-(4-(3-cloro-4-fluoroanilino)-7-metoxiquinazolin-5-iloxi)piperidin-1-il)acetato

Carbonato de potasio (343 mg), cloroacetato de metilo (0.036 ml), y 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (ejemplo 13) (100 mg) en DMF (2 ml) se agitaron y calentaron en un tubo sellado a 120°C usando una fuente concentrada de microondas. Seguidamente la mezcla se enfrió, se vertió en agua, y se extrajo en DCM (que contenía 2% metanol), se secó sobre sulfato de sodio y se concentró *in*

h
501

vacuo. El aceite crudo resultante se purificó por cromatografía, usando 0-5% metanol en DCM. Esto produjo el compuesto del título como un aceite incoloro (72 mg, 61%); Espectro NMR (CDCl_3) 2.05 (m, 2H), 2.30 (m, 2H), 2.57 (m, 2H), 2.98 (m, 2H), 3.31 (s, 2H), 3.73 (s, 3H), 3.92 (s, 3H), 4.60 (m, 1H), 6.51 (d, 1H), 6.85 (d, 1H), 7.13 (t, 1H), 7.46 (m, 1H), 8.02 (dd, 1H), 8.56 (s, 1H), 9.79 (s, 1H); Espectro de masa MH^+ 475.

El procedimiento descrito arriba se repitió usando el halogenuro de alquilo apropiado y amina. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 17.1

4-(4-(3-Cloro-4-fluoroanilino)-7-metoxiquinazolin-5-iloxi) piperidin-1-ilmetil metil cetona

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (ejemplo 13) con clorometil metil cetona en 44% de rendimiento; Espectro NMR (CDCl_3) 2.05 (m, 2H), 2.16 (s, 3H), 2.29 (m, 2H), 2.46 (m, 2H), 2.88 (m, 2H), 3.27 (s, 2H), 3.92 (s, 3H), 4.59 (m, 1H), 6.51 (d, 1H), 6.85 (d, 1H), 7.14 (t, 1H), 7.45 (m, 1H), 8.01 (dd, 1H), 8.57 (s, 1H), 9.79 (s, 1H); Espectro de masa MH^+ 459.

Ejemplo 17.2

2-(4-(4-(3-Cloro-4-fluoroanilino)-7-metoxiquinazolin-5-iloxi) piperidin-1-il)acetamida

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina (ejemplo 13) con 2-bromoacetamida en 43% de rendimiento; Espectro NMR (DMSO-d_6) 1.99 (m, 2H), 2.18 (m, 2H), 2.32 (m, 2H), 2.90 (s, 2H), 3.92 (s, 3H), 4.83 (m, 1H), 6.84 (s, 2H), 7.10 (bs, 1H), 7.25 (bs, 1H), 7.47 (t, 1H), 7.57 (m, 1H), 8.31 (dd, 1H), 8.51 (s, 1H), 9.95 (s, 1H); Espectro de masa MH^+ 460.

Ejemplo 18

4-(3-Cloro-4-fluoroanilino)-5-(1-(metanosulfonil)piperidin-4-iloxi)-7-metoxi-quinazolina

Cloruro de metanosulfonilo (42 mg) se agregó a una solución agitada de 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina

(ejemplo 13) (100 mg) y trietilamina (55 mg) en DCM (20 ml) a temperatura ambiente. Después de 1 hora, la mezcla de reacción se diluyó con DCM, se lavó con carbonato hidrogenado de sodio acuoso saturado, se secó sobre sulfato de sodio y se concentró *in vacuo* para proporcionar el material crudo, el cual se trituró bajo metanol para proporcionar el compuesto del título como un sólido blanco (85 mg, 71%); Espectro NMR (CDCl_3) 2.08 (m, 2H), 2.37 (m, 2H), 2.79 (s, 3H), 3.19 (m, 2H), 3.67 (m, 2H), 3.92 (s, 3H), 4.71 (m, 1H), 6.51 (d, 1H), 6.87 (d, 1H), 7.14 (t, 1H), 7.37 (m, 1H), 8.00 (dd, 1H), 8.56 (s, 1H), 9.58 (s, 1H); Espectro de masa MH^+ 481.

Ejemplo 19

Clorhidrato de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(3-(1-metilpiperazin-4-il)propoxi)-5-ciclopentiloxiquinazolina

Una solución de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(3-cloropropoxi)-5-ciclopentiloxiquinazolina (Ejemplo de Referencia 21.8) (0.15 g) y 1-metilpiperazina (0.18 ml) en NMP (2 ml) se calentó a 80°C durante 16 horas. La solución se concentró *in vacuo* y el residuo se trituró con éter. El sólido resultante se filtró para proporcionar el compuesto del título como un sólido blanco (30 mg, 18%); Espectro de masa MH^+ 620.

El procedimiento descrito arriba se repitió usando el halogenuro de alquilo apropiado y amina. Así se obtuvieron los compuestos descritos a continuación:

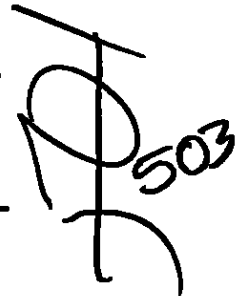
Ejemplo 19.1

Clorhidrato de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(3-(N-(2-metoxietil)-N-metilamino)propoxi)-5-ciclopentiloxiquinazolina

Obtenido haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(3-cloropropoxi)-5-ciclopentiloxiquinazolina (Ejemplo de Referencia 21.8) y N-(2-metoxietil)-N-metilamina en 60% de rendimiento; Espectro de masa MH^+ 609.

Ejemplo 19.2

Clorhidrato de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(2-(1-metilpiperazin-4-il)etoxi)-5-ciclopentiloxiquinazolina



Obtenido haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(2-cloroetoxi-5-ciclopentiloxiquinazolina (Ejemplo de Referencia 21.9) y 1-metilpiperazina en 62% de rendimiento; Espectro de masa MH^+ 606.

Ejemplo 19.3

4-(3-Cloro-4-fluoroanilino)-7-(3-(pirrolidin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar pirrolidina y 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) en 64% de rendimiento; Espectro NMR (DMSO- d_6) 1.67 (m, 4H), 1.92 (m, 2H), 2.15 (m, 1H), 2.30 (m, 1H), 2.45 (m, 4H), 2.55 (t, 2H), 3.78 - 3.98 (m, 3H), 4.15 - 4.20 (m, 3H), 5.45 (m, 1H), 6.80 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.47 (s, 1H), 9.87 (s, 1H); Espectro de masa MH^+ 488.

Ejemplo 19.4

4-(3-Cloro-4-fluoroanilino)-7-(3-piperidinopropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y piperidina en 64% de rendimiento; Espectro NMR (DMSO- d_6) 1.38 (m, 2H), 1.48 (m, 4H), 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.40 (m, 7H), 3.78 - 3.98 (m, 3H), 4.10 - 4.20 (m, 3H), 5.45 (m, 1H), 6.79 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.85 (s, 1H); Espectro de masa MH^+ 502.

Ejemplo 19.5

4-(3-Cloro-4-fluoroanilino)-7-(3-morfolinopropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y morfolina en 64% de rendimiento; Espectro NMR (DMSO- d_6) 1.92 (m, 2H), 2.18 (m, 1H), 2.22 - 2.45 (m, 7H), 3.58 (m, 4H), 3.78 - 3.98 (m, 3H), 4.10 - 4.20 (m, 3H), 5.48 (m, 1H), 6.79 (m, 2H), 7.41



(t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.83 (s, 1H); Espectro de masa MH^+ 504.

Ejemplo 19.6

4-(3-Cloro-4-fluoroanilino)-7-(3-(N-metil-N-(2-propinil)amino)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y N-metil-N-propargilamina en 53% de rendimiento; Espectro NMR (DMSO- d_6) 1.88 (m, 2H), 2.18 (m, 1H), 2.20 (s, 3H), 2.22 - 2.40 (m, 1H), 2.50 (m, 2H), 3.08 (t, 1H), 3.28 (m, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.20 (m, 3H), 5.48 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.83 (s, 1H); Espectro de masa MH^+ 486.

Ejemplo 19.7

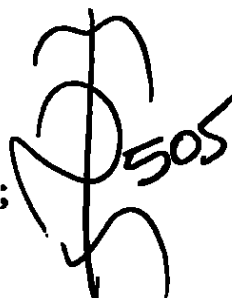
4-(3-Cloro-4-fluoroanilino)-7-(3-(N-metil-N-alilamino)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y N-metil-N-alilamina en 37% de rendimiento; Espectro NMR (DMSO- d_6) 1.90 (m, 2H), 2.10 - 2.20 (m, 4H), 2.22 - 2.40 (m, 1H), 2.45 (m, 2H), 2.98 (d, 2H), 3.78-3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.05 - 5.20 (m, 2H), 5.48 (m, 1H), 5.80 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.83 (s, 1H); Espectro de masa MH^+ 488.

Ejemplo 19.8

4-(3-Cloro-4-fluoroanilino)-7-(3-(4-hidroxipiperidin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y 4-hidroxipiperidina en 78% de rendimiento; Espectro NMR (DMSO- d_6) 1.38 (m, 2H), 1.70 (m, 2H), 1.90 (m, 2H), 2.01 (m, 2H), 2.18 (m, 2H), 2.32 (m, 1H), 2.40 (m, 2H), 2.70 (m, 2H), 3.42 (m, 1H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 4.50 (m, 1H), 5.48 (m, 1H), 6.80 (m,



2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H);

Espectro de masa MH^+ 518.

Ejemplo 19.9

4-(3-Cloro-4-fluoroanilino)-7-(3-(3-oxo-piperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y piperazin-2-ona en 76% de rendimiento; Espectro NMR (DMSO- d_6) 1.90 (m, 2H), 2.18 (m, 1H), 2.32 (m, 1H), 2.45 - 2.60 (m, 4H), 2.95 (s, 2H), 3.15 (m, 2H), 3.78 - 3.98 (m, 3H), 4.13 - 4.21 (m, 3H), 5.48 (m, 1H), 6.80 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 7.70 (s, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH^+ 517.

Ejemplo 19.10

4-(3-Cloro-4-fluoroanilino)-7-(3-(4-metilpiperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y 1-metilpiperazina en 41% de rendimiento; Espectro NMR (DMSO- d_6) 1.90 (m, 2H), 2.10 - 2.20 (m, 4H), 2.21 - 2.42 (m, 11H), 3.78 - 3.98 (m, 3H), 4.13 - 4.21 (m, 3H), 5.48 (m, 1H), 6.80 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH^+ 517.

Ejemplo 19.11

4-(3-Cloro-4-fluoroanilino)-7-(3-(4-(2-metoxietil)piperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y 4-(2-metoxietil)piperazina en 49% de rendimiento; Espectro NMR (DMSO- d_6) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.45 (m, 13H), 3.20 (s, 3H), 3.40 (t, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.48 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH^+ 561.

**Ejemplo 19.12****4-(3-Cloro-4-fluoroanilino)-7-(3-(4-(N,N-dimetilcarbamoilmetil)piperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y 1-(N,N-dimetilcarbamoilmetil)piperazina en 62% de rendimiento; Espectro NMR (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 11H), 2.78 (s, 3H), 2.99 (s, 3H), 3.27 (s, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.48 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH⁺ 588.

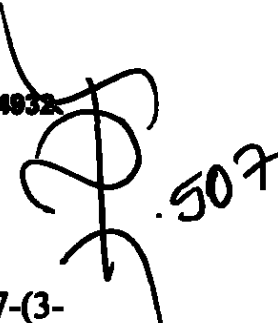
Ejemplo 19.13**4-(3-Cloro-4-fluoroanilino)-7-(3-(4-alilpiperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y 1-alilpiperazina en 50% de rendimiento; Espectro NMR (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 11H), 2.90 (d, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.10 (m, 2H), 5.45 (m, 1H), 5.78 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH⁺ 543.

Ejemplo 19.14**4-(3-Cloro-4-fluoroanilino)-7-(3-(4-(2-propinil)piperazin-1-il) propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y 1-(2-propinil)piperazina en 53% de rendimiento; Espectro NMR (DMSO-d₆) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 11H), 3.08 (t, 1H), 3.22 (d, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.47 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH⁺ 541.

Ejemplo 19.15**4-(3-Cloro-4-fluoroanilino)-7-(3-(4-cianometilpiperazin-1-il) propoxi)-**

**5-(tetrahydrofurano-3-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y 1-cianometilpiperazina en 40% de rendimiento; Espectro NMR (DMSO-d6) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 11H), 3.68 (s, 2H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.47 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH^+ 542.

Ejemplo 19.16**4-(3-Cloro-4-fluoroanilino)-7-(3-(piperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21) y piperazina en 71% de rendimiento; Espectro NMR (DMSO-d6) 1.90 (m, 2H), 2.18 (m, 1H), 2.22 - 2.50 (m, 7H), 2.70 (m, 4H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.47 (m, 1H), 6.79 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH^+ 503.

Ejemplo 19.17**4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-(4-metilpiperazin-1-il)propoxi)quinazolina**

Obtenida haciendo reaccionar 1-metilpiperazina y 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-cloropropil-1-iloxi)quinazolina (Ejemplo de Referencia 21.10) en 41% de rendimiento; Espectro NMR (CDCl₃) 2.0 (m, 4H), 2.2 - 2.4 (m, 10H), 2.4 - 2.6 (m, 10H), 2.8 (m, 2H), 4.1 (t, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.3 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 649.

Ejemplo 19.18**4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-piperidinopropoxi)quinazolina**

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-

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fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-cloropropil-1-iloxi)quinazolina (Ejemplo de Referencia 21.10) con piperidina en 44% de rendimiento; Espectro NMR (CDCl₃) 1.5 (m, 2H), 1.6 (m, 4H), 2.0 (m, 4H), 2.2 - 2.4 (m, 11H), 2.5 (m, 2H), 2.8 (m, 2H), 4.1 (t, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 634.

Ejemplo 19.19

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-morfolinopropoxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-cloropropil-1-iloxi)quinazolina (Ejemplo de Referencia 21.10) con morfolina en 39% de rendimiento; Espectro NMR (CDCl₃) 2.0 - 2.2 (m, 4H), 2.3 (m, 2H), 2.4 (s, 3H), 2.5 - 2.6 (m, 7H), 2.8 (m, 2H), 3.6 (d, 1H), 3.8 (m, 4H), 4.2 (t, 2H), 4.6 (m, 1H) 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.4 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 636.

Ejemplo 19.20

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-(N-(2-metoxietil)-N-metilamino)propoxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-cloropropil-1-iloxi)quinazolina (Ejemplo de Referencia 21.10) con N-(2-metoxietil)-N-metilamina en 35% de rendimiento; Espectro NMR (CDCl₃) 2.0 (m, 4H), 2.2 - 2.4 (m, 10H), 2.6 (m, 4H), 2.8 (m, 2H), 3.3 (s, 3H), 3.5 (t, 2H), 4.1 (t, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 638.

Ejemplo 19.21

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(2-(4,4-difluoropiperidin-1-il)etoxi)quinazolina

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Obtenida haciendo reaccionar 4,4-difluoropiperidina y 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(2-cloroetoxi)quinazolina (Ejemplo de Referencia 21.11) en 23% de rendimiento; Espectro NMR (CDCl₃) 1.9-2.1 (m, 6H), 2.3 (m, 2H), 2.8 (t, 4H), 3.0 (t, 2H), 3.6 (m, 2H), 4.1 (dt, 2H), 4.3 (t, 2H), 4.8 (m, 1H) 5.2 (s, 2H), 6.6 (d, 1H), 7.0 (d, 1H), 7.0 (m, 2H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.8 (d, 1H), 8.6 (s, 1H), 9.9 (s, 1H); Espectro de masa MH⁺ 643.

Ejemplo 19.22

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(3-(N-(2-metoxietil)-N-metilamino)propoxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(3-cloropropil-1-iloxi)quinazolina (Ejemplo de Referencia 21.12) con N-(2-metoxietil)-N-metilamina en 52% de rendimiento; Espectro NMR (DMSO-d₆) 1.8 - 2.0 (m, 2H), 2.0 - 2.2 (m, 4H), 2.7 (m, 3H), 3.1 (m, 4H), 3.3 (s, 3H), 3.6 (m, 2H), 3.7 (m, 2H), 3.9 (m, 2H), 4.2 (m, 2H), 5.0 (m, 1H), 5.3 (s, 2H), 6.9 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH⁺ 625.

Ejemplo 19.23

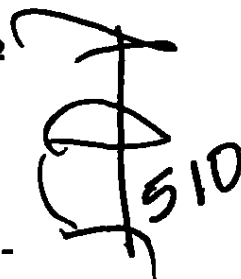
4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(3-piperidinopropoxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(3-cloropropil-1-iloxi)quinazolina (Ejemplo de Referencia 21.12) con piperidina en 39% de rendimiento; Espectro NMR (DMSO-d₆) 1.6 (m, 2H), 1.8 - 2.0 (m, 6H), 2.2 (m, 4H), 3.2 (m, 6H), 3.6 (t, 2H), 4.0 (m, 2H), 4.3 (m, 2H), 5.0 (m, 1H), 5.3 (s, 2H), 6.9 (s, 2H), 7.2 - 7.4 (m, 4H), 7.5 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH⁺ 621.

Ejemplo 19.24

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(2-(4-metilpiperazin-1-il)etoxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-



fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(2-cloroetoxi)quinazolina (Ejemplo de Referencia 21.11) con 1-metilpiperazina en 43% de rendimiento; Espectro NMR (CDCl₃) 1.9 (m, 2H), 2.2 - 2.3 (m, 5H), 2.5 (m, 4H), 2.6 (m, 4H), 2.9 (t, 2H), 3.6 (m, 2H), 4.1 (dt, 2H), 4.2 (t, 2H), 4.7 (m, 1H) 5.1 (s, 2H), 6.6 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 622.

Ejemplo 19.25

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(3-(4-metil-piperazin-1-il)propoxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-(3-cloropropil-1-iloxi)quinazolina (Ejemplo de Referencia 21.12) con 1-metilpiperazina en 59% de rendimiento; Espectro NMR (CDCl₃) 2.0 (m, 4H), 2.3 (m, 5H), 2.4 - 2.6 (m, 10H), 3.6 (m, 2H); 4.1 (dt, 2H), 4.1 (t, 2H), 4.8 (m, 1H), 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 636.

Ejemplo 19.26

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(3-(4-metil-piperazin-1-il)propoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 1-metilpiperazina con 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(3-cloropropiloxi)-5-(tetrahidrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21.13) en 43% de rendimiento; Espectro NMR (DMSO-d₆) 2.0 (m, 2H), 2.2 (m, 5H), 2.3 - 2.5 (m, 10H), 3.8 - 4.0 (m, 3H), 4.2 (m, 3H), 5.3 (s, 2H) 5.5 (m, 1H), 6.8 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 - 7.6 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH⁺ 622.

Ejemplo 19.27

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(3-piperidinopropoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-

fluorobenciloxi)anilino)-7-(3-cloropropiloxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (**Ejemplo de Referencia 21.13**) con piperidina en 23% de rendimiento; Espectro NMR (DMSO-d₆) 1.4 (m, 2H), 1.5 - 1.6 (m, 4H), 1.9 - 2.0 (m, 2H), 2.2 - 2.3 (m, 1H), 2.3 - 2.5 (m, 7H), 3.8 - 4.0 (m, 3H), 4.2 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.1-7.4 (m, 4H), 7.5 (m, 1H), 7.6 (dd, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH⁺ 607.

Ejemplo 19.28

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahydrofurano-3-iloxi)-7-(2-(4-metil-piperazin-1-il)etoxi)quinazolina

Obtenida haciendo reaccionar 1-metilpiperazina con 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(2-cloroetoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (**Ejemplo de Referencia 21.14**) en 53% de rendimiento; Espectro NMR (DMSO-d₆) 2.2 - 2.3 (m, 4H), 2.3 - 2.4 (m, 5H), 2.5 (m, 2H - oculto bajo la señal DMSO), 2.8 (m, 2H), 3.4 (m, 2H - parcialmente oscurecido por la señal de agua), 3.8 - 4.0 (m, 3H), 4.2 - 4.3 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.9 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5-7.6 (m, 2H), 8.2 (m, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH⁺ 622.

Ejemplo 19.29

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(3-morfolinopropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-(3-cloropropiloxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (**Ejemplo de Referencia 21.13**) con morfolina en 14% de rendimiento; Espectro NMR (DMSO-d₆) 2.0 (m, 2H), 2.2 (m, 1H), 2.3 - 2.5 (m, 7H), 3.6 (m, 4H), 3.8 - 4.0 (m, 3H), 4.2 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 - 7.6 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Espectro de masa MH⁺ 609.

Ejemplo 19.30

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(2-morfolinoetoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 7-(2-cloroetoxi)-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahydrofurano-3-iloxi)quinazolina (**Ejemplo**

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de Referencia 21.14) con morfolina en 33% de rendimiento; Espectro NMR (DMSO-d6) 2.2 (m, 1H), 2.4 (m, 1H), 2.5 (m, 2H - oculto bajo la señal DMSO), 2.8 (t, 2H), 3.3 (m, 2H - parcialmente oscurecido por la señal de agua), 3.6 (m, 4H), 3.8 - 4.0 (m, 3H), 4.2 (d, 1H), 4.3 (t, 2H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.2-7.4 (m, 4H), 7.5 (m, 1H), 7.6 (dd, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH^+ 595.

Ejemplo 19.31

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(2-[N-(2-metoxietil)-N-metilamino]etoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 7-(2-cloroetoxi)-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21.14) con N-(2-metoxietil)-N-metilamina en 25% de rendimiento; Espectro NMR (DMSO-d6) 2.2 (m, 1H), 2.3 (s, 3H), 2.7 (t, 2H), 2.9 (t, 2H), 3.3 (s, 3H), 3.3 (m, 1H), 3.5 (t, 2H), 3.8 - 4.0 (m, 3H), 4.2 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 - 7.6 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH^+ 597.

Ejemplo 19.32

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(2-piperidinoetoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 7-(2-cloroetoxi)-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 21.14) con piperidina en 34% de rendimiento; Espectro NMR (DMSO-d6) 1.4 (m, 2H), 1.5 - 1.6 (m, 4H), 2.2 - 2.3 (m, 1H), 2.3 - 2.4 (m, 1H), 2.5 (m, 2H), 2.8 (m, 2H), 3.2 (m, 2H), 3.9 - 4.0 (m, 3H), 4.2 - 4.3 (m, 3H), 5.3 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.2 - 7.4 (m, 4H), 7.5 (m, 1H), 7.6 (dd, 1H), 8.2 (d, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH^+ 593.

Ejemplo 20

4-(3-Cloro-4-fluoroanilino)-7-(3-(4-acetilpiperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina

Se agregaron trietilamina (38 μ l) y anhídrido acético (26 μ l), cada uno en una porción, a una solución agitada de 4-(3-cloro-4-fluoroanilino)-7-

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(3-(piperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina (ejemplo 19.16) (115 mg) en DCM (2 ml) a 0°C. La solución se agitó a 0°C bajo una atmósfera de nitrógeno durante 1 hora y luego se agregaron DCM (10 ml) y carbonato hidrogenado de sodio acuoso saturado (15 ml). Las capas se separaron y la capa acuosa se extrajo con DCM (2 x 10 ml). Se secaron los extractos orgánicos combinados y se concentraron *in vacuo* para dejar un sólido blanco, el cual se purificó por cromatografía usando 0 - 8% 7N amoníaco en metanol en DCM como eluyente. Esto produjo el compuesto del título como un sólido blanco (105 mg, 84%); Espectro NMR (DMSO-d6) 1.90 - 2.00 (m, 5H), 2.18 (m, 1H), 2.22 - 2.50 (m, 7H), 3.42 (m, 4H), 3.78 - 3.98 (m, 3H), 4.10 - 4.21 (m, 3H), 5.47 (m, 1H), 6.80 (m, 2H), 7.41 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.93 (s, 1H); Espectro de masa MH^+ 545.

Ejemplo 21

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(1-metilpiperidin-4-ilmetoxi)quinazolina

4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-(piperidin-4-ilmetoxi)quinazolina (130 mg) (ejemplo 13.2) se agregó a una mezcla de ácido fórmico (0.58 ml) y formaldehído (37% en peso solución acuosa, 0.88 ml), y la mezcla resultante se calentó a 85°C durante 2 horas. Se agregó un exceso de solución de carbonato hidrogenado de sodio acuoso saturado, y el producto se extrajo en DCM. Se secaron los extractos orgánicos combinados y se concentraron *in vacuo* para proporcionar el producto crudo, el cual se trituró bajo metanol frío para proporcionar el compuesto del título como un sólido blanco (20 mg, 15%); Espectro NMR (CDCl₃) 1.5 (m, 2H), 1.8 (m, 3H), 2.0 (m, 4H), 2.2 - 2.4 (m, 10H), 2.8 (m, 2H), 2.9 (m, 2H), 3.9 (d, 2H), 4.6 (m, 1H) 5.1 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 6.9 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH^+ 620.

Ejemplo 22

4-(1-(2-Cianobenzil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

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Hidruro de sodio (13.1 mg) se agregó a una solución de 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.8) (120 mg) en DMA (1 ml), y se agitó a temperatura ambiente durante 30 minutos. Esta mezcla se agregó entonces gota a gota a una solución de 2-clorometilbenzonitrilo (50 mg) en DMA (1 ml), y se dejó agitar durante 5 horas a temperatura ambiente. Se agregó exceso de agua, lo cual generó el producto como una goma espesa, que se extrajo por decantación. La goma se purificó entonces por cromatografía, usando 0-10% metanol en DCM como eluyente para proporcionar el producto como una goma, la cual se trituró bajo agua, para proporcionar el compuesto del título como un sólido (10 mg, 6%); Espectro de masa MH^+ 519.

El procedimiento descrito arriba se repitió usando el halogenuro de alquilo apropiado. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo 22.1

4-(1-(3-Fluorobenzil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.8) con 3-fluorocloruro de bencilo en 14% de rendimiento; Espectro de masa MH^+ 512.

Ejemplo 22.2

4-(1-(2-Fluorobenzil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.8) con 2-fluorocloruro de bencilo en 5% de rendimiento; Espectro de masa MH^+ 512.

Ejemplo 22.3

4-(1-(5-metilisoxazol-3-ilmetil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida haciendo reaccionar 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.8) con 3-(clorometil)-5-metilisoxazol en 74% de rendimiento; Espectro de masa MH^+ 499.

Ejemplo 22.4**4-(1-Bencilindol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.8) con cloruro de bencilo en 46% de rendimiento; Espectro de masa MH^+ 494.

Ejemplo 22.5**7-Metoxi-5-(1-metilpiperidin-4-iloxi)-4-(1-(2-piridilmetil)indol-5-ilamino)quinazolina**

Obtenida haciendo reaccionar 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.8) con cloruro de 2-picolilo en 35% de rendimiento; Espectro de masa MH^+ 495.

Ejemplo 22.6**7-Metoxi-5-(1-metilpiperidin-4-iloxi)-4-(1-(tiazol-4-ilmetil)indol-5-ilamino)quinazolina**

Obtenida haciendo reaccionar 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.8) con 4-(clorometil)tiazol en 57% de rendimiento; Espectro de masa MH^+ 501.

Ejemplo 22.7**4-(1-(2,6-Difluorobenzil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenida haciendo reaccionar 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina (ejemplo 2.8) con 2,6-difluorocloruro de bencilo en 43% de rendimiento; Espectro de masa MH^+ 530. **Ejemplo 23**

Los compuestos mostrados en negrilla en Tabla 1 se prepararon en la siguiente forma:

Aminas (1.2 mM) se disolvieron en NMP (1 ml) y 50 μ l de cada solución se pasaron a una placa de 96 pozos. Se prepararon soluciones patrón de los 4 sustratos;

Sustrato	A	4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 21.2) (120mg);
Sustrato	B	7-(2-cloroetoxi)-4-(3-cloro-4-fluoroanilino)-5-(1-

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metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 21.6) (116mg);

Sustrato C 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahidropiran-4-iloxi)quinazolina (Ejemplo de Referencia 21.3) (117mg) y

Sustrato D 7-(2-cloroetoxi)-4-(3-cloro-4-fluoroanilino)-5-(tetrahidropiran-4-iloxi)quinazolina (Ejemplo de Referencia 21.7) (113 mg) en NMP (1.25 ml), y se agregaron alícuotas de 50 µl a cada pozo que contenía la solución de amina mostrada en Tabla 1. La placa se calentó y se agitó a 80° C durante 60 horas, se dejó enfriar, luego se concentró *in vacuo*. A cada pozo se agregó DMSO (550 µl). Se tomaron entonces alícuotas de 50 µl de cada pozo para determinación de la pureza LCMS. Se determinó la pureza LCMS en una columna Phenomenex Synergi (sílice de fase reversa, 50 x 2 mm, caudal 1.1 ml/minuto), eluyendo con acetonitrilo-agua que contenía ácido fórmico (0.05%) en una gradiente de 5-95% durante 4.5 minutos, con detección UV a 254 nm. Así se obtuvo el compuesto mostrado en negrilla en Tabla 1.

Tabla 1

En tabla 1, EG se refiere a Ejemplo, RT se refiere al tiempo de retención LCMS (minutos)

EG	Compuesto	M-H ⁺	RT
23.1	<u>4-(3-Cloro-4-fluoroanilino)-7-[3-(N-(2-hidroxietyl)-N-metilamino)propoxi]-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con N-(2-hidroxietyl)-N-metilamina	517	0.84
23.2	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-(3-hidroxi-pirrolidin-1-il)propoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con 3-hidroxi-pirrolidina	528	0.86

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EG	Compuesto	M-H ⁺	RT
23.3	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-(4-metilpiperazin-1-il)propoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con 1-metilpiperazina	542	0.93
23.4	<u>4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-piperidinopropoxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con piperidina	527	0.96
23.5	<u>4-(3-Cloro-4-fluoroanilino)-7-[3-(N-metil-N-(1-metilpirrolidin-3-il)amino)propoxi]-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con N-(1-metilpirrolidin-3-il)-N-metilamina	556	0.88
23.6	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-(4-(2-metoxietil)piperazin-1-il)propoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con 1-(2-metoxietil)piperazina	586	0.98
23.7	<u>4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-pirrolidin-1-ilpropoxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con pirrolidina	513	0.90
23.8	<u>4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-morfolinopropoxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con morfolina	529	1.06
23.9	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-homopiperidin-1-ilpropoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con homopiperidina	542 (MH ⁺)	1.00
23.10	<u>4-(3-Cloro-4-fluoroanilino)-7-[3-(N-(2-dimetilaminoetil)-N-metilamino)propoxi]-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato A con N,N,N'-trimetiletilen diamina	544	0.97

EG	Compuesto	M-H ⁺	RT
23.11	4-(3-Cloro-4-fluoroanilino)-7-(3-(4-metilhomopiperazin-1-il)propoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato A con 1-metilhomopiperazina	555 (MH ⁺)	0.92
23.12	4-(3-Cloro-4-fluoroanilino)-7-[2-(N-(2-hidroxietil)-N-metilamino)etoxi]-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato B con N-(2-hidroxietil)-N-metilamina	503	0.77
23.13	<u>4-(3-Cloro-4-fluoroanilino)-7-(2-(3-hidroxipirrolidin-1-il)etoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato B con 3-hidroxipirrolidina	515	0.76
23.14	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-metilpiperazin-1-il)etoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato B con 1-metilpiperazina	528	0.84
23.15	4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-piperidinoetoxi)quinazolina Obtenida haciendo reaccionar Sustrato B con piperidina	514 (M ⁺)	1.01
23.16	4-(3-Cloro-4-fluoroanilino)-7-[2-(N-metil-N-(1-metilpirrolidin-3-il)amino)etoxi]-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato B con N-(1-metilpirrolidin-3-il)-N-metilamina	544 (MH ⁺)	0.90
23.17	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-(2-metoxietil)piperazin-1-il)etoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato B con 1-(2-metoxietil)piperazina	574 (MH ⁺)	1.06

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EG	Compuesto	M-H ⁺	RT
23.18	4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-pirrolidin-1-iletoxi)quinazolina Obtenida haciendo reaccionar Sustrato B con pirrolidina	499	0.89
23.19	4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-morfolinoetoxi)quinazolina Obtenida haciendo reaccionar Sustrato B con morfolina	515	1.22
23.20	4-(3-Cloro-4-fluoroanilino)-7-(2-homopiperidin-1-iletoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato B con homopiperidina	527	1.03
23.21	4-(3-Cloro-4-fluoroanilino)-7-[2-(N-(2-dimetilaminoetil)-N-metilamino)etoxi]-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato B con N,N,N'-trimetiletilen diamina	530	0.93
23.22	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-metilhomopiperazin-1-il)etoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato B con 1-metilhomopiperazina	544 (MH ⁺)	0.96
23.23	4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-(4-isopropilpiperazin-1-il)etoxi)quinazolina Obtenida haciendo reaccionar Sustrato B con 1-isopropilpiperazina	556	0.99
23.24	4-(3-Cloro-4-fluoroanilino)-7-[2-(N-(2-metoxietil)-N-metilamino)etoxi]-5-(1-metilpiperidin-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato B con N-(2-metoxietil)-N-metilamina	517	0.95

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EG	Compuesto	M-H ⁺	RT
23.25	4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-(4-(2-morfolinoetil)piperazin-1-il)etoxi)quinazolina Obtenida haciendo reaccionar Sustrato B con 1-(2-morfolino-etil)piperazina	627	1.04
23.26	<u>4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-(4-(tetrahidrofurano-2-ilmetil)piperazin-1-iletoxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato B con 1-(tetrahidrofurano-2-il-metil)piperazina	598	1.10
23.27	<u>4-(3-Cloro-4-fluoroanilino)-7-(2-(3-dimetilaminopirrolidin-1-il)etoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato B con 3-dimetilaminopirrolidina	542	0.98
23.28	<u>4-(3-Cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-[2-(4-(1-metilpiperidin-4-il)piperazin-1-il)etoxi]quinazolina</u> Obtenida haciendo reaccionar Sustrato B con 1-(1-metilpiperidin-4-il)piperazina	611	1.08
23.29	<u>4-(3-Cloro-4-fluoroanilino)-7-[3-(N-(2-hidroxietil)-N-metilamino)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato C con N-(2-hidroxietil)-N-metilamina	505 (MH ⁺)	1.56
23.30	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-(3-hidroxipirrolidin-1-il)propoxi)-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato C con 3-hidroxipirrolidina	516	1.54

EG	Compuesto	M-H ⁺	RT
23.31	4-(3-Cloro-4-fluoroanilino)-7-(3-(4-metilpiperazin-1-il)propoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con 1-metilpiperazina	531 (MH ⁺)	1.64
23.32	4-(3-Cloro-4-fluoroanilino)-7-(3-piperidinopropoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con piperidina	514	1.64
23.33	4-(3-Cloro-4-fluoroanilino)-7-[3-(4-(2-metoxietil)piperazin-1-il)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con 1-(2-metoxietil)piperazina	574 (MH ⁺)	1.68
23.34	4-(3-Cloro-4-fluoroanilino)-7-(3-pirrolidin-1-ilpropoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con pirrolidina	500	1.59
23.35	4-(3-Cloro-4-fluoroanilino)-7-(3-morfolinopropoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con morfolina	516	1.85
23.36	4-(3-Cloro-4-fluoroanilino)-7-[3-(N-(2-dimetilaminoetil)-N-metilamino)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con 1,1,2-trimetiletilen diamina	531	1.67
23.37	4-(3-Choro-4-fluoroanilino)-7-(3-(4-metilhomopiperazin-1-il)propoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con 1-metilhomopiperazina	543	1.55

EG	Compuesto	M-H ⁺	RT
23.38	4-(3-Cloro-4-fluoroanilino)-7-(3-(4-isopropilpiperazin-1-il)propoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con 1-isopropilpiperazina	557	1.66
23.39	4-(3-Cloro-4-fluoroanilino)-7-[3-(N-(2-metoxietil)-N-metilamino)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con N-(2-metoxietil)-N-metilamina	518	1.64
23.40	4-(3-Cloro-4-fluoroanilino)-7-[3-(4-(2-morfolinoetil)piperazin-1-il)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con 1-(2-morfolinoetil)piperazina	628	1.40
23.41	4-(3-Cloro-4-fluoroanilino)-7-[3-(4-(tetrahydrofurano-2-ilmetil)piperazin-1-il)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con 1-(tetrahydrofurano-2-il-metil)piperazina	601 (MH ⁺)	1.76
23.42	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-(3-dimetilaminopirrolidin-1-il)propoxi)-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato C con 3-dimetilaminopirrolidina	545 (MH ⁺)	1.61
23.43	4-(3-Cloro-4-fluoroanilino)-7-[3-(4-(1-metilpiperidin-4-il)piperazin-1-il)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato C con 1-(1-metilpiperidin-4-il)piperazina	612	1.27

EG	Compuesto	M-H ⁺	RT
23.44	<u>4-(3-Cloro-4-fluoroanilino)-7-[2-(N-(2-hidroxietil)-N-metilamino)etoxi]-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato D con N-(2-hidroxietil)-N-metilamina	490	1.53
23.45	<u>4-(3-Cloro-4-fluoroanilino)-7-(2-(4-metilpiperazin-1-il)etoxi)-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato D con 1-metilpiperazina	515	1.59
23.46	<u>4-(3-Cloro-4-fluoroanilino)-7-(2-piperidinoetoxi)-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato D con piperidina	500	1.64
23.47	<u>4-(3-Cloro-4-fluoroanilino)-7-[2-(N-metil-N-(1-metilpirrolidin-3-il)amino)etoxi]-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato D con N-(1-metilpirrolidin-3-il)-N-metilamina	529	1.54
23.48	<u>4-(3-Cloro-4-fluoroanilino)-7-(2-(4-(2-metoxietil)piperazin-1-il)etoxi)-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato D con 1-(2-metoxietil)piperazina	559	1.66
23.49	<u>4-(3-Cloro-4-fluoroanilino)-7-(2-(homopiperidin-1-il)etoxi)-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato D con homopiperidina	514	1.69
23.50	<u>4-(3-Cloro-4-fluoroanilino)-7-[2-(N-(2-dimetilaminoetil)-N-metilamino)etoxi]-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenido haciendo reaccionar Sustrato D con N,N,N'-trimetiletilen diamina	517	1.60

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EG	Compuesto	M-H ⁺	RT
23.51	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-metilhomopiperazin-1-il)etoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato D con 1-metilhomopiperazina	529	1.60
23.52	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-isopropilpiperazin-1-il)etoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato D con 1-isopropilpiperazina	543	1.61
23.53	4-(3-Cloro-4-fluoroanilino)-7-[2-(N-metil-N-(2-metoxietil)amino)etoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato D con N-(2-metoxietil)-N-metilamina	504	1.65
23.54	4-(3-Cloro-4-fluoroanilino)-7-[2-(4-(2-morfolinoetil)piperazin-1-il)etoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato D con 1-(2-morfolinoetil)piperazina	616 (MH ⁺)	1.48
23.55	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-(2-tetrahidrofurano-2-ilmetil)piperazin-1-il)etoxi)-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato D con 1-(tetrahidrofurano-2-il-metil)piperazina	587 (MH ⁺)	1.71
23.56	4-(3-Cloro-4-fluoroanilino)-7-[2-(3-dimetilaminopirrolidin-1-il)etoxi]-5-(tetrahidropiran-4-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato D con 3-dimetilaminopirrolidina	529	1.59
23.57	<u>4-(3-Cloro-4-fluoroanilino)-7-[2-(4-(1-metilpiperidin-4-il)piperazin-1-il)etoxi]-5-(tetrahidropiran-4-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato D con 1-(1-	598	1.35

EG	Compuesto	M-H ⁺	RT
	metilpiperidin-4-il)piperazina		

Ejemplo 24

Los compuestos mostrados en negrilla en Tabla 2 se prepararon en la siguiente forma:

Aminas (1.2 mM) se disolvieron en NMP (1 ml) y 50 µl de cada solución se pasaron a una placa de 96 pozos. Se prepararon soluciones patrón de los 4 sustratos;

Sustrato E 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina (**Ejemplo de Referencia 21**) (113mg);

Sustrato F 7-(2-cloroetoxi)-4-(3-cloro-4-fluoroanilino)-5-(tetrahidrofurano-3-iloxi)quinazolina (**Ejemplo de Referencia 21.4**) (110 mg);

Sustrato G 4-(3-cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-ciclopentiloxiquinazolina (**Ejemplo de Referencia 21.1**) (113mg) y

Sustrato H 7-(2-cloroetoxi)-4-(3-cloro-4-fluoroanilino)-5-ciclopentiloxiquinazolina (**Ejemplo de Referencia 21.5**) (109mg) en NMP (1.25 ml), y se agregaron alícuotas de 50 µl a cada pozo que contenía la solución de amina mostrada en Tabla 2. La placa se calentó y se agitó a 80°C durante 60 horas, se dejó enfriar, luego se concentró *in vacuo*. A cada pozo se agregó DMSO (550 µl). Seguidamente se tomaron alícuotas de 50 µl de cada pozo para determinación de pureza LCMS. Se determinó la pureza LCMS en una columna Phenomenex Synergi (sílice de fase reversa, 50 x 2 mm, caudal 1.1 ml/minuto), eluyendo con acetonitrilo-agua que contenía ácido fórmico (0.05%) en una gradiente de 5-95% durante 4.5 minutos, con detección UV a 254 nm. Así se obtuvieron los compuestos mostrados en negrilla en Tabla 2.

Tabla 2

En Tabla 2 EG se refiere a Ejemplo, RT se refiere al tiempo de retención LCMS (minutos)

EG	Compuesto	M-H ⁺	RT
24.1	4-(3-Cloro-4-fluoroanilino)-7-[3-(N-(2-hidroxietyl)-N-metilamino)propoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con N-(2-hidroxietyl)-N-metilamina	490	1.09
24.2	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-(3-hidroxi-pirrolidin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato E con 3-hidroxi-pirrolidina	502	1.14
24.3	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-(4-metilpiperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato E con 1-metilpiperazina	515	1.08
24.4	4-(3-Cloro-4-fluoroanilino)-7-(3-piperidinopropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con piperidina	500	1.20
24.5	4-(3-Cloro-4-fluoroanilino)-7-[3-(4-(2-metoxietil)piperazin-1-il)propoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con 1-(2-metoxietil)piperazina	559	1.13
24.6	<u>4-(3-Cloro-4-fluoroanilino)-7-(3-pirrolidin-1-ilpropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina</u> Obtenida haciendo reaccionar Sustrato E con pirrolidina	486	1.19
24.7	4-(3-Cloro-4-fluoroanilino)-7-(3-morfolinopropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con morfolina	502	1.14
24.8	4-(3-Cloro-4-fluoroanilino)-7-(3-homopiperidin-1-ilpropoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con homopiperidina	514	1.26

EG	Compuesto	M-H ⁺	RT
24.9	4-(3-Cloro-4-fluoroanilino)-7-[3-(N-(2-dimetilaminoetil)-N-metilamino)propoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con N,N,N'-trimetiletilen diamina	517	0.94
24.10	4-(3-Cloro-4-fluoroanilino)-7-(3-(4-metilhomopiperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con 1-metilhomopiperazina	529	0.91
24.11	4-(3-Cloro-4-fluoroanilino)-7-(3-(4-isopropilpiperazin-1-il)propoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con 1-isopropilpiperazina	543	1.12
24.12	4-(3-Cloro-4-fluoroanilino)-7-[3-(N-(2-metoxietil)-N-metilamino)propoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con N-(2-metoxietil)-N-metilamina	504	1.19
24.13	4-(3-Cloro-4-fluoroanilino)-7-[3-(4-(2-morfolinoetil)piperazin-1-il)propoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con 1-(2-morfolinoetil)piperazina	614	0.93
24.14	4-(3-Cloro-4-fluoroanilino)-7-[3-(4-(tetrahydrofurano-2-ilmetil)piperazin-1-il)propoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con 1-(tetrahydrofurano-2-il-metil)piperazina	585	1.18

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EG	Compuesto	M-H ⁺	RT
24.15	4-(3-Cloro-4-fluoroanilino)-7-[3-(3-dimetilaminopirrolidin-1-il)propoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con 3-dimetilaminopirrolidina	529	0.94
24.16	4-(3-Cloro-4-fluoroanilino)-7-[3-(4-(1-metilpiperidin-4-il)piperazin-1-il)propoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato E con 1-(1-metilpiperidin-4-il)piperazina	598	0.92
24.17	4-(3-Cloro-4-fluoroanilino)-7-[2-(N-(2-hidroxietil)-N-metilamino)etoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con N-(2-hidroxietil)-N-metilamina	477 (MH ⁺)	1.12
24.18	4-(3-Cloro-4-fluoroanilino)-7-[2-(3-hidroxipirrolidin-1-il)etoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con 3-hidroxipirrolidina	488	1.12
24.19	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-metilpiperazin-1-il)etoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con 1-metilpiperazina	501	1.09
24.20	4-(3-Cloro-4-fluoroanilino)-7-(2-piperidinoetoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con piperidina	486	1.19
24.21	4-(3-Cloro-4-fluoroanilino)-7-[2-(4-(2-metoxietil)piperazin-1-il)etoxi]-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con 1-(2-metoxietil) piperazina	545	1.15
24.22	<u>4-(3-Cloro-4-fluoroanilino)-7-(2-pirrolidin-1-iletoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina</u>	472	1.15



EG	Compuesto	M-H ⁺	RT
	Obtenida haciendo reaccionar Sustrato F con pirrolidina		
24.23	4-(3-Cloro-4-fluoroanilino)-7-(2-morfolinoetoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con morfolina	488	1.15
24.24	4-(3-Cloro-4-fluoroanilino)-7-(2-homopiperidin-1-iletoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con homopiperidina	499	1.28
24.25	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-metilhomopiperazin-1-il)etoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con 1-metilhomopiperazina	515	0.98
24.26	4-(3-Cloro-4-fluoroanilino)-7-(2-(4-isopropilpiperazin-1-il)etoxi)-5-(tetrahydrofurano-3-iloxi)quinazolina Obtenida haciendo reaccionar Sustrato F con 1-isopropilpiperazina	529	1.15
24.27	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-(3-pirrolidin-1-ilpropoxi)quinazolina Obtenida haciendo reaccionar Sustrato G con pirrolidina	484	1.45
24.28	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-(3-morfolinopropoxi)quinazolina Obtenida haciendo reaccionar Sustrato G con morfolina	500	1.42
24.29	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-(3-homopiperidin-1-ilpropoxi)quinazolina Obtenida haciendo reaccionar Sustrato G con homopiperidina	512	1.54
24.30	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-(3-(4-metilhomopiperazin-1-il)propoxi)quinazolina Obtenida haciendo reaccionar Sustrato G con 1-metilhomopiperazina	527	1.17

530

EG	Compuesto	M-H ⁺	RT
24.31	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[3-(4-isopropilpiperazin-1-il)propoxi]quinazolina Obtenida haciendo reaccionar Sustrato G con 1-isopropilpiperazina	541	1.39
24.32	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[3-(N-(2-metoxietil)-N-metilamino)propoxi]quinazolina Obtenida haciendo reaccionar Sustrato G con N-(2-metoxietil)-N-metilamina	502	1.47.
24.33	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[3-(4-(2-morfolinoetil)piperazin-1-il)propoxi]quinazolina Obtenida haciendo reaccionar Sustrato G con 1-(2-morfolinoetil)piperazina	612	1.16
24.34	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[3-(4-(tetrahidrofurano-2-ilmetil)piperazin-1-il)propoxi]quinazolina Obtenida haciendo reaccionar Sustrato G con 1-(tetrahidrofurano-2-il-metil)piperazina	583	1.45
24.35	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[3-(3-dimetilaminopirrolidin-1-il)propoxi]quinazolina Obtenida haciendo reaccionar Sustrato G con 3-dimetilaminopirrolidina	527	1.18
24.36	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[3-(4-(1-metilpiperidin-4-il)piperazin-1-il)propoxi]quinazolina Obtenida haciendo reaccionar Sustrato G con 1-(1-metilpiperidin-4-il)piperazina	596	1.16
24.37	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[2-(N-(2-hidroxietil)-N-metilamino)etoxi]quinazolina Obtenida haciendo reaccionar Sustrato H con N-(2-hidroxietil)-N-metilamina	474	1.35

Handwritten signature and initials, possibly 'JD' and '531'.

EG	Compuesto	M-H ⁺	RT
24.38	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[2-(3-hidroxipirrolidin-1-il)etoxi]quinazolina Obtenida haciendo reaccionar Sustrato H con 3-hidroxipirrolidina	486	1.37
24.39	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-(2-(4-metilpiperazin-1-il)etoxi)quinazolina Obtenida haciendo reaccionar Sustrato H con 1-metilpiperazina	499	1.37
24.40	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-(2-piperidinoetoxi)quinazolina Obtenida haciendo reaccionar Sustrato H con piperidina	484	1.47
24.41	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[2-(4-(2-metoxietil)piperazin-1-il)etoxi]quinazolina Obtenida haciendo reaccionar Sustrato H con 1-(2-metoxietil)piperazina	543	1.40
24.42	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-(2-homopiperidin-1-iletoxi)quinazolina Obtenida haciendo reaccionar Sustrato H con homopiperidina	498	1.52
24.43	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[2-(4-metilhomopiperazin-1-il)etoxi]quinazolina Obtenida haciendo reaccionar Sustrato H con 1-metilhomopiperazina	513	1.21
24.44	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[2-(4-(2-morfolinoetil)piperazin-1-il)etoxi]quinazolina Obtenida haciendo reaccionar Sustrato H con 1-(2-morfolinoetil)piperazina	598	1.14
24.45	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[2-(4-(tetrahydrofurano-2-ilmetil)piperazin-1-il)etoxi]quinazolina Obtenida haciendo reaccionar Sustrato H con 1-(tetrahydrofurano-2-il-metil)piperazina	569	1.45

EG	Compuesto	M-H ⁺	RT
24.46	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[2-(3-dimetilaminopirrolidin-1-il)etoxi]quinazolina Obtenida haciendo reaccionar Sustrato H con 3-dimetilaminopirrolidina	513	1.20
24.47	4-(3-Cloro-4-fluoroanilino)-5-ciclopentiloxi-7-[2-(4-(1-metilpiperidin-4-il)piperazin-1-il)etoxi]quinazolina Obtenida haciendo reaccionar Sustrato H con 1-(1-metilpiperidin-4-il)piperazina	582	1.13

Ejemplo 25

Composición Farmacéutica

Lo siguiente ilustra una forma de administración farmacéutica representativa de la invención como se define aquí (denominándose el ingrediente activo "Compuesto X"), para uso terapéutico o profiláctico en humanos:

(a)	Tableta I	mg/tableta
	Compuesto X.....	100
	Lactosa Ph.Eur	182.75
	Croscarmelosa sódica	12.0
	Pasta almidón de maíz (5% p/v pasta).....	2.25
	Estearato de magnesio	3.0
(b)	Inyección I	(50 mg/ml)
	Compuesto X.....	5.0% p/v
	1M Solución hidróxido de sodio.....	15.0% v/v
	0.1M Ácido clorhídrico (para ajustar pH a 7.6)	
	Polietilen glicol 400	4.5% p/v
	Agua para inyección a 100%.	

Las anteriores formulaciones pueden obtenerse por procedimientos tradicionales bien conocidos en el arte farmacéutico. Por ejemplo, la tableta puede prepararse combinando los componentes entre sí y comprimiendo la mezcla en una tableta.

Materiales Iniciales

Ejemplo de Referencia 1

4, 6 -Difluoroisatina

Una solución de clorhidrato de hidroxilamina (41.7 g) en agua (100 ml) se agregó gota a gota a una solución de hidrato cloral (31.6 g) y sulfato de sodio (228.3 g) en agua (50 ml) a 60°C. La solución resultante se agregó entonces a una solución de 3,5-difluoroanilina (25 g) en agua (300 ml) y HCl concentrado (16 ml) a 80°C, y la mezcla se calentó a 95°C durante 15 minutos. El sólido blanco resultante se filtró y se lavó con agua. Este sólido se agregó en porciones a H₂SO₄ concentrado (167 ml) a 60 - 80°C, para proporcionar una solución roja profunda la cual se agitó durante 15 minutos más. La solución se vertió en agua helada y se filtró el sólido anaranjado resultante, se lavó con agua, y se secó *in vacuo* para producir el compuesto del título (24.64 g, 69%); Espectro NMR (DMSO-d₆) 6.58 (dd, 1H), 6.85 (dt, 1H), 11.36 (bs, 1H); Espectro de masa M-H⁺ 182.

Ejemplo de Referencia 2

4,6-Dibenciloxiisatina

Clorhidrato de 3,5-dibenciloxianilina (Ejemplo de Referencia 24) (32.33 g) se agregó cuidadosamente a cloruro de oxalilo (100 ml) y la solución se calentó a reflujo durante 3 horas. La solución se enfrió y se concentró *in vacuo*. Se agregó metanol (100 ml) al residuo y la mezcla se calentó a reflujo durante 1 hora. La reacción se dejó enfriar, y el precipitado resultante se filtró y se lavó con metanol para proporcionar el compuesto del título como un sólido amarillo (16.22 g, 48%); Espectro NMR (DMSO-d₆) 5.22 (s, 2H), 5.24 (s, 2H), 6.10 (s, 1H), 6.38 (s, 1H), 7.30-7.50 (m, 10H), 10.90 (bs, 1H); Espectro de masa M-H⁺ 358.

El procedimiento descrito arriba se repitió usando el clorhidrato de anilina apropiado. Así se obtuvo el compuesto descrito a continuación:



Ejemplo de Referencia 2.1

4,6-Dimetoxiisatina

Obtenida de clorhidrato de 3,5-dimetoxianilina; Espectro NMR (DMSO-d6) 3.83 (s, 3H), 3.86 (s, 3H), 6.00 (d, 1H), 6.17 (d, 1H), 10.86 (bs, 1H).

Ejemplo de Referencia 3

Ácido 2-amino-4,6-difluorobenzoico

4,6-Difluoroisatina (Ejemplo de Referencia 1) (10 g) se disolvió en 33 % (p/v) NaOH acuoso (85 ml) a 75°C. A esta solución se agregó H₂O₂ (30%, 16 ml) gota a gota durante 30 minutos. La reacción se agitó durante 1 hora a 75°C, luego se enfrió a temperatura ambiente. Se agregó hielo, y la mezcla de reacción se acidificó a pH 1 con HCl concentrado. Se filtró el precipitado resultante, se lavó con agua y se secó *in vacuo* para proporcionar el compuesto del título como un sólido amarillo pálido (6.28 g, 66%) Espectro de masa M⁺ 173.

El procedimiento descrito arriba se repitió usando la isatina apropiada. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 3.1

Ácido 2-amino-4,6-dibenciloxibenzoico

Obtenido de 4,6-dibenciloxiisatina (Ejemplo de Referencia 2) en 87% de rendimiento; Espectro NMR (DMSO-d6) 4.97 (s, 2H), 5.05 (s, 2H), 5.92 (d, 1H), 5.97 (d, 1H), 7.20 - 7.50 (m, 10H).

Ejemplo de Referencia 3.2

Ácido 2-amino-4,6-dimetoxibenzoico

Obtenido de 4, 6-dimetoxiisatina (Ejemplo de Referencia 2.1) en 63% de rendimiento; Espectro NMR (DMSO-d6) 3.69 (s, 3H), 3.75 (s, 3H), 5.77 (d, 1H), 5.92 (d, 1H); Espectro de masa MH⁺ 198.

Ejemplo de Referencia 4

Metil 2-amino-4,6-difluorobenzoato

Sulfato de dimetilo (11.76 ml) se agregó gota a gota a una mezcla de carbonato de potasio (37.8 g) y ácido 2-amino-4,6-difluorobenzoico (Ejemplo de Referencia 3) (21.56 g) en DMF (500 ml) a 0°C. La reacción

se agitó durante 1 hora, luego se vertió en agua. El precipitado resultante se filtró, se lavó con agua y se secó *in vacuo* para proporcionar el compuesto del título como un sólido beige (9.39 g, 40%). El filtrado se extrajo con acetato de etilo, y los extractos orgánicos combinados se secaron y se concentraron *in vacuo* para producir más del compuesto del título como un sólido cristalino amarillo (6.57 g, 28%); Espectro NMR (DMSO-d₆) 3.78 (s, 3H), 6.25 (m, 1H), 6.38 (m, 1H), 6.90 (bs, 2H).

El procedimiento descrito arriba se repitió usando el ácido apropiado. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 4.1

Metil 2-amino-4,6-dibenciloxibenzoato

Obtenido de ácido 2-amino-4,6-dibenciloxibenzoico (Ejemplo de Referencia 3.1) en 81% de rendimiento; Espectro NMR (DMSO-d₆) 3.72 (s, 3H), 5.02 (s, 2H), 5.07 (s, 2H), 5.96 (s, 1H), 6.03 (s, 1H), 6.20 (bs, 2H), 7.22 - 7.48 (m, 10H). Espectro de masa MH⁺ 364.

Ejemplo de Referencia 4.2

Metil 2-amino-4,6-dimetoxibenzoato

Obtenido de ácido 2-amino-4,6-dimetoxibenzoico (Ejemplo de Referencia 3.2) en 77% de rendimiento; Espectro NMR (DMSO-d₆) 3.66 (s, 3H), 3.67 (s, 3H), 3.68 (s, 3H), 5.75 (d, 1H), 5.90 (d, 1H), 6.13 (s, 2H).

Ejemplo de Referencia 5

5,7-Difluoro-3,4-dihidroquinazolin-4-ona

Una solución de 2-amino-4,6-difluorobenzoato de metilo (Ejemplo de Referencia 4) (15.96 g) y acetato de formamidina (19.58 g) en 2-metoxietanol (200 ml) se calentó a 120°C durante 16 horas. La reacción se enfrió, se concentró *in vacuo*, y el residuo se trituró con metanol para proporcionar el compuesto del título como un sólido beige (8.09 g, 52%); Espectro NMR (DMSO-d₆) 7.20 - 7.40 (m, 2H), 8.10 (s, 1H), 12.35 (bs, 1H). Espectro de masa M-H⁺ 181.

El procedimiento descrito arriba se repitió usando el éster antranílico apropiado. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 5.1

5,7-Dibenciloxi-3,4-dihidroquinazolin-4-ona

Obtenida de 2-amino-4,6-dibenciloxibenzoato de metilo (Ejemplo de Referencia 4.1) en 64% de rendimiento; Espectro NMR (DMSO-d6) 5.20 (s, 4H), 6.72 (d, 1H), 6.78 (d, 1H), 7.20 - 7.60 (m, 10H), 7.92 (s, 1H), 11.70 (bs, 1H); Espectro de masa M-H⁺ 357.

Ejemplo de Referencia 5.2**3,4-Dihidro-5,7-dimetoxiquinazolin-4-ona**

Obtenida de 2-amino-4,6-dimetoxibenzoato de metilo (Ejemplo de Referencia 4.2) en 88% de rendimiento; Espectro NMR (DMSO-d6) 3.80 (s, 3H), 3.84 (s, 3H), 6.51 (d, 1H), 6.63 (d, 1H), 7.88 (s, 1H), 11.62 (bs, 1H); Espectro de masa MH⁺ 207.

Ejemplo de Referencia 6**5-Benciloxi-3,4-dihidro-7-fluoroquinazolin-4-ona**

Hidruro de sodio (0.88 g, 60% dispersión en aceite mineral) se agregó en porciones durante 5 minutos a alcohol bencílico (1.71 ml) en DMF (30 ml) a 0°C. La reacción se agitó a 0°C durante 10 minutos, a continuación se agregó 5,7-difluoro-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 5) (2.00 g) en porciones durante 5 minutos. La solución resultante se dejó calentar a temperatura ambiente y se agitó durante 12 horas. La mezcla de reacción se concentró *in vacuo*, se agregó agua (10 ml) y luego se extrajo con acetato de etilo (100 ml). Se precipitó un sólido de la capa orgánica y éste se filtró y se secó *in vacuo* para proporcionar el compuesto del título como agujas blancas (1.00 g, 34%). Se extrajo la capa acuosa con acetato de etilo (3 x 100ml), se secó, se filtró y se concentró *in vacuo* para proporcionar más del compuesto del título (0.64 g, 22%); Espectro NMR (DMSO-d6) 5.23 (s, 2H), 6.90 (dd, 1H), 7.00 (dd, 1H), 7.30 (t, 1H), 7.36 (t, 2H), 7.58 (d, 2H), 8.00 (s, 1H), 11.96 (bs, 1H); Espectro de masa MH⁺ 271.

El procedimiento descrito arriba se repitió usando el alcohol apropiado. Así se obtuvo el compuesto descrito a continuación:

Ejemplo de Referencia 6.1**7-Flu ro-5-(tetrahidropiran-4-il xi)-3,4-dihidroquinazolin-4-ona**

Obtenida de 5,7-difluoro-3,4-dihidroquinazolina (Ejemplo de Referencia 5) y tetrahidropiran-4-ol en 38% de rendimiento; Espectro NMR (CDCl₃) 1.92 (m, 2H), 2.08 (m, 2H), 3.64 (m, 2H), 4.10 (m, 2H), 4.70 (m, 1H), 6.67 (dd, 1H), 7.00 (dd, 1H), 8.00 (s, 1H); Espectro de masa MH⁺ 265.

Ejemplo de Referencia 7

5-(1-Metilpiperidin-4-iloxi)-3,4-dihidroquinazolin-4-ona

Hidruro de sodio (4.1 g, 60%) se agregó en porciones a 4-hidroxi-1-metilpiperidina (10.7 g) en DMA (125 ml). La reacción se agitó a temperatura ambiente durante 15 minutos, 50°C durante 15 minutos luego se dejó enfriar a temperatura ambiente. Se agregó en una porción única 5-fluoro-3,4-dihidroquinazolin-4-ona (5.1 g), y la mezcla se calentó a 80°C durante 2 horas. La reacción se enfrió, se concentró *in vacuo* y el residuo se purificó por cromatografía usando DCM - 7N amoníaco en metanol (9:1) como eluyente para proporcionar el compuesto del título como un sólido blanco luego de la trituración con éter (7.3 g, 91%); Espectro NMR (DMSO-d₆) 1.72 (m, 2H), 1.88 (m, 2H), 2.15 (s, 3H), 2.19 (m, 2H), 2.63 (m, 2H), 4.46 (m, 1H), 7.00 (d, 1H), 7.14 (d, 1H), 7.61 (t, 1H), 7.91 (s, 1H), 11.75 (bs, 1H).

El procedimiento descrito arriba se repitió usando el alcohol apropiado. Así se obtuvo el compuesto descrito a continuación:

Ejemplo de Referencia 7.1

5-(1-*tert*-Butoxicarbonilpiperidin-4-iloxi)-3,4-dihidroquinazolin-4-ona

Obtenida de 1-*tert*-butoxicarbonil-4-hidroxipiperidina en 87% de rendimiento; Espectro NMR (DMSO-d₆) 1.39 (s, 9H), 1.6 - 1.87 (m, 4H), 3.32 - 3.43 (m, 2H), 3.47 - 3.60 (m, 2H), 4.75 (m, 1H), 7.08 (d, 1H), 7.17 (d, 1H), 7.64 (t, 1H) 8.84 (s, 1H), 11.80 (bs, 1H); Espectro de masa MH⁺ 346.

Ejemplo de Referencia 8

Trifluoroacetato de 5-hidroxi-7-fluoro-3,4-dihidroquinazolin-4-ona

Ácido trifluoroacético (50 ml) se agregó a 5-benciloxi-7-fluoro-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 6) (1.64 g) y la solución

amarillo pálido resultante se calentó a 70°C durante 2 horas. La mezcla de reacción se concentró *in vacuo* para proporcionar un aceite. Éter dietílico se agregó para proporcionar un sólido, el cual se filtró para proporcionar el compuesto del título como un sólido rosado (820 mg, 75%); Espectro NMR (DMSO-d₆) 6.72 (dd, 1H), 7.86 (dd, 1H), 8.12 (s, 1H), 12.13 (bs, 1H); Espectro de masa MH⁺ 181.

Ejemplo de Referencia 9

7-Benciloxi-3,4-dihidro- 5-hidroxiquinazolin-4-ona

Bromuro de magnesio (4.3 g) se agregó cuidadosamente a 5,7-dibenciloxi-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 5.1) (8.37 g) en piridina (250 ml) y la solución se calentó a reflujo durante 1 hora. La mezcla de reacción se enfrió, se concentró *in vacuo* y el residuo se trituró con agua y se filtró para producir el compuesto del título como sólido blancuzco (6.2 g, 99%); Espectro de masa MH⁺ 269.

El procedimiento descrito arriba se repitió usando la 5-alcoxiquinazolina apropiada. Así se obtuvo el compuesto descrito a continuación:

Ejemplo de Referencia 9.1

3,4-Dihidro-5-hidroxi-7-metoxiquinazolin-4-ona

Obtenida de 3,4-dihidro-5,7-dimetoxiquinazolin-4-ona (Ejemplo de Referencia 5.2) en 93% de rendimiento: Espectro de masa MH⁺ 193.

Ejemplo de Referencia 10

4-(3-Cloro-4-fluoroanilino)-5-hidroxi-7-metoxiquinazolina

Se agregó clorhidrato de piridina (1.08 g) a 4-(3-cloro-4-fluoroanilino)-5,7-dimetoxiquinazolina (Ejemplo de Referencia 19.1) (3.29 g) suspendida en piridina (50 ml). La reacción se calentó a 115°C durante 8 horas, luego se dejó enfriar a temperatura ambiente. El precipitado formado al enfriar se filtró y se lavó con agua antes de secar bajo succión para proporcionar el compuesto del título como un sólido amarillo (2.21 g, 70%); Espectro NMR (DMSO-d₆) 3.8 (s, 3H), 6.4 (d, 2H), 7.4 (t, 1H), 7.6 (m, 1H), 8.0 (d, 1H), 8.5 (s, 1H); Espectro de masa MH⁺ 320.

Ejemplo de Referencia 11**3,4-Dihidro-5-hidroxi-7-(3-(R)-dimetilaminopirrolidin-1-il)quinazolin-4-ona**

3-(R)-(+)-Dimetilaminopirrolidina (490 μ l) se agregó a trifluoroacetato de 3,4-dihidro-5-hidroxi-7-fluoroquinazolin-4-ona (Ejemplo de Referencia 8) (400 mg) suspendido en NMP (400 μ l). La solución resultante se calentó a 100°C durante 3 horas. La mezcla de reacción se concentró *in vacuo* para proporcionar un aceite marrón. Se agregó metanol (500 μ l) y la suspensión se filtró para proporcionar el compuesto del título como un sólido rosado (243 mg, 41%); Espectro NMR (DMSO-d₆) 1.80 (m, 1H), 2.18 (s, 6H), 2.78 (m, 1H), 3.05 (dd, 1H), 3.24 (m, 2H), 3.47 (m, 2H), 6.00 (d, 1H), 6.10 (d, 1H), 7.88 (s, 1H), 11.85 (bs, 2H), Espectro de masa MH⁺ 273.

El procedimiento descrito arriba se repitió usando la 7-fluoroquinazolina y amina apropiadas. Así se obtuvo el compuesto descrito a continuación:

Ejemplo de Referencia 11.1**3,4-Dihidro-7-(3-(S)-dimetilaminopirrolidin-1-il)-5-(tetrahidropiran-4-iloxi)quinazolin-4-ona**

Obtenida de 3,4-dihidro-7-fluoro-5-(tetrahidropirani-4-oxi)quinazolin-4-ona (Ejemplo de Referencia 6.1) y 3-(S)-dimetilaminopirrolidina en 74% de rendimiento; Espectro NMR (DMSO-d₆) 1.66 (m, 2H), 1.90 (m, 2H), 2.20 (s, 6H), 2.77 (m, 1H), 3.07 (t, 1H), 3.26 (m, 3H), 3.40 - 3.58 (m, 4H), 3.90 (m, 2H), 4.65 (m, 1H), 6.20 (s, 2H), 7.75 (s, 1H); Espectro de masa MH⁺ 359.

Ejemplo de Referencia 12**7-(3-(R)-Dimetilaminopirrolidin-1-il)-5-hidroxi-3-pivaloiloimetil-3,4-dihidroquinazolin-4-ona**

Hidruro de sodio (40 mg) se agregó en porciones durante 5 minutos a 3,4-dihidro-5-hidroxi-7-(3-(R)-dimetilaminopirrolidin-1-il)quinazolin-4-ona (Ejemplo de Referencia 11) (0.24 g) en DMF (5 ml) a 0°C. Se agregó pivalato de clorometilo (130 μ l) gota a gota durante 15 minutos para

proporcionar una solución anaranjada clara. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas más. Se observó una reacción incompleta por tlc; por lo tanto, se enfrió la reacción a 0°C y se agregó hidruro de sodio (10 mg) seguido por pivalato de clorometilo (26 µl). Se concluyó la reacción después de agitar durante 1 hora a temperatura ambiente. La mezcla de reacción se concentró *in vacuo* y se purificó por cromatografía usando 2-10% metanol en DCM como eluyente para proporcionar el compuesto del título como un sólido crema (210 mg, 62%); Espectro NMR (DMSO-d₆) 1.10 (s, 9H), 1.83 (m, 1H), 2.22 (s, 6H), 2.81 (m, 1H), 3.13 (m, 1H), 3.33 (m, 2H), 3.45 - 3.60 (m, 2H), 5.80 (s, 2H), 6.08 (d, 1H), 6.18 (d, 1H), 8.21 (s, 1H), 11.39 (s, 1H): Espectro de masa MH⁺ 389.

El procedimiento descrito arriba se repitió usando la 3,4-dihidroquinazolin-4-ona apropiada. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 12.1

5-Hidroxi-7-metoxi-3-pivaloiloximetil-quinazolin-4-ona

Obtenida de 3,4-dihidro-5-hidroxi-7-metoxiquinazolin-4-ona (Ejemplo de Referencia 9.1) en 67% de rendimiento; Espectro NMR (DMSO-d₆) 1.11 (s, 9H), 3.85 (s, 3H), 5.86 (s, 2H), 6.51 (d, 1H), 6.66 (d, 1H), 8.37 (s, 1H), 11.42 (s, 1H): Espectro de masa M-H⁺ 305.

Ejemplo de Referencia 12.2

7-Benciloxi-5-hidroxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona

Obtenida de 7-benciloxi-3,4-dihidro-5-hidroxiquinazolin-4-ona (Ejemplo de Referencia 9) en 93% de rendimiento; Espectro NMR (DMSO-d₆) 1.11 (s, 9H), 5.23 (s, 2H), 5.86 (s, 2H), 6.59 (d, 1H), 6.74 (d, 1H), 7.29 - 7.47 (m, 5H), 8.37 (s, 1H), 11.42 (s, 1H): Espectro de masa M-H⁺ 383.

Ejemplo de Referencia 13

7-(3-(R)-Dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona

7-(3-(R)-Dimetilaminopirrolidin-1-il)-5-hidroxi-3-pivaloiloximetil-

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3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12) (210 mg), 4-hidroxi-*N*-metilpiperidina (125 mg) y trifenilfosfina (280 mg) se disolvieron en DCM anhidro (10 ml), bajo una atmósfera de nitrógeno a 0°C. Una solución de azodicarboxilato de di-*tert*-butilo (250 mg) en DCM (1 ml) se agregó gota a gota durante 5 minutos y la solución amarilla resultante se dejó calentar a temperatura ambiente y se agitó durante 18 horas. Se agregó 1 equivalente más de todos los reactivos en la misma secuencia de arriba bajo las mismas condiciones de reacción y se dejó agitar durante 12 horas más a temperatura ambiente. La mezcla de reacción se concentró *in vacuo* y el residuo se purificó por cromatografía usando 2-8% metanol en DCM como eluyente para proporcionar el compuesto del título como un sólido crema (200 mg, 77%); Espectro de masa MH^+ 486.

El procedimiento descrito arriba se repitió usando la 5-hidroxiquinazolina y el alcohol apropiados. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 13.1

7-Metoxi-3-pivaloiloximetil-5-(tetrahydrofurano-3-iloxi)-3,4-dihidroquinazolin-4-ona

Obtenida de 5-hidroxi-7-metoxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12.1) y tetrahydrofurano-3-ol en 80% de rendimiento; Espectro de masa MH^+ 377.

Ejemplo de Referencia 13.2

7-Metoxi-3-pivaloiloximetil-5-(tetrahidropiran-4-iloxi)-3,4-dihidroquinazolin-4-ona

Obtenida de 5-hidroxi-7-metoxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12.1) y tetrahidropiran-4-ol en 70% de rendimiento; Espectro NMR (DMSO- d_6) 1.11 (s, 9H), 1.66 (m, 2H), 1.92 (m, 2H), 3.49 (m, 2H), 3.85 (s, 3H), 3.89 (m, 2H), 4.76 (m, 1H), 5.81 (s, 2H), 6.68 (s, 2H), 8.30 (s, 1H).

Ejemplo de Referencia 13.3

7-Benciloxi-3-pivaloiloximetil-5-(tetrahidropiran-4-iloxi)-3,4-dihidroquinazolin-4-ona

Obtenida de 7-benciloxi-5-hidroxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12.2) y tetrahidropiran-4-ol en 80% de rendimiento; Espectro de masa MH^+ 467.

Ejemplo de Referencia 13.4

7-Benciloxi-5-(1-metilpiperidin-4-iloxi)-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona

Obtenida de 7-benciloxi-5-hidroxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12.2) y 1-metilpiperidin-4-ol en 100% de rendimiento; Espectro de masa MH^+ 480.

Ejemplo de Referencia 13.5

7-Metoxi-5-(1-metilpiperidin-4-iloxi)-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona

Obtenida de 5-hidroxi-7-metoxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12.1) y 1-metilpiperidin-4-ol en 56% de rendimiento; Espectro NMR (DMSO- d_6) 1.11 (s, 9H), 1.71 (m, 2H), 1.87 (m, 2H), 2.13 (s, 3H), 2.18 (m, 2H), 2.57 (m, 2H), 3.84 (s, 3H), 4.52 (m, 1H), 5.79 (s, 2H), 6.61 (d, 1H), 6.67 (d, 1H), 8.16 (s, 1H); Espectro de masa MH^+ 405.

Ejemplo de Referencia 13.6

7-Benciloxi-3-pivaloiloximetil-5-(tetrahydrofurano-3-iloxi)-3,4-dihidroquinazolin-4-ona

Obtenida de 7-benciloxi-5-hidroxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12.2) tetrahydrofurano-3-ol en 83% de rendimiento; Espectro de masa MH^+ 454.

Ejemplo de Referencia 13.7

7-Benciloxi-5-ciclopentiloxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona

Obtenida de 7-benciloxi-5-hidroxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12.2) y ciclopentanol en 88% de rendimiento; Espectro de masa MH^+ 451.

Ejemplo de Referencia 14

3,4-Dihidro-7-(3-(R)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-

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4-il xi)quinazolin-4-ona

7N amoníaco en metanol (20 ml) se agregó a 7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 13) (200 mg) y la solución se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró *in vacuo* para proporcionar un aceite, el cual se trituró con éter dietílico para proporcionar un sólido anaranjado, que se filtró para proporcionar el compuesto del título (100 mg, 66%); Espectro NMR (DMSO-*d*₆) 1.72 (m, 3H), 1.87 (m, 3H), 2.10 (m, 3H), 2.15 (s, 3H), 2.18 (s, 6H), 2.63 (m, 2H), 2.75 (m, 1H), 3.05 (dd, 1H), 3.26 (m, 1H), 3.30 - 3.50 (m, 2H), 4.35 (m, 1H), 6.08 (s, 1H), 6.12 (s, 1H), 7.67 (s, 1H), 11.07 (bs, 1H); Espectro de masa MH⁺ 370.

El procedimiento descrito arriba se repitió usando la 3-pivaloiloximetilquinazolona apropiada. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 14.1**3,4-Dihidro-7-metoxi-5-(tetrahydrofurano-3-iloxi)quinazolin-4-ona**

Obtenida de 7-metoxi-3-pivaloiloximetil-5-(tetrahydrofurano-3-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 13.1) en 87% de rendimiento; Espectro de masa MH⁺ 263.

Ejemplo de Referencia 14.2**3,4-Dihidro-7-metoxi-5-(tetrahidropiran-4-iloxi)quinazolin-4-ona**

Obtenida de 7-metoxi-3-pivaloiloximetil-5-(tetrahidropiran-4-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 13.2) en 91% de rendimiento; Espectro NMR (DMSO-*d*₆) 1.65 (m, 2H), 1.91 (m, 2H), 3.48 (m, 2H), 3.83 (s, 3H), 3.89 (m, 2H), 4.70 (m, 1H), 6.60 (d, 2H), 6.65 (d, 2H), 7.88 (s, 1H), 12.12 (bs, 1H); Espectro de masa M-H⁺ 275.

Ejemplo de Referencia 14.3**7-Benciloxi-3,4-dihidro-5-(tetrahidropiran-4-iloxi)quinazolin-4-ona**

Obtenida de 7-benciloxi-3-pivaloiloximetil-5-(tetrahidropiran-4-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 13.3) en 76% de rendimiento; Espectro de masa MH⁺ 263.

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Ejemplo de Referencia 14.4**7-Benciloxi-3,4-dihidro-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona**

Obtenida de 7-benciloxi-5-(1-metilpiperidin-4-iloxi)-3-pivaloiloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 13.4) en 48% de rendimiento; Espectro de masa MH^+ 366.

Ejemplo de Referencia 14.5**3,4-Dihidro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona**

Obtenida de 7-metoxi-5-(1-metilpiperidin-4-iloxi)-3-pivaloiloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 13.5) en 75% de rendimiento; Espectro NMR (DMSO- d_6) 1.68 (m, 2H), 1.84 (m, 2H), 2.11 (s, 3H), 2.18 (m, 2H), 2.61 (m, 2H), 3.82 (s, 3H), 4.45 (m, 1H), 6.53 (d, 2H), 6.64 (d, 2H), 7.86 (s, 1H), 11.60 (bs, 1H); Espectro de masa MH^+ 290.

Ejemplo de Referencia 14.6**7-Benciloxi-3,4-dihidro-5-(tetrahidrofurano-3-iloxi)quinazolin-4-ona**

Obtenida de 7-benciloxi-3-pivaloiloiloximetil-5-(tetrahidrofurano-3-iloxi)-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 13.6) en 86% de rendimiento; Espectro NMR (DMSO- d_6) 2.00 (m, 1H), 2.17 (m, 1H), 3.81 (m, 4H), 5.05 (m, 1H), 5.21 (s, 2H), 6.54 (d, 1H), 6.75 (d, 1H), 7.40 (m, 5H), 7.87 (s, 1H), 11.67 (bs, 1H); Espectro de masa MH^+ 339.

Ejemplo de Referencia 14.7**7-Benciloxi-5-ciclopentiloxi-3,4-dihidroquinazolin-4-ona**

Obtenida de 7-benciloxi-5-ciclopentiloxi-3-pivaloiloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 13.7) en 88% de rendimiento; Espectro de masa MH^+ 337.

Ejemplo de Referencia 15**5-(1-*tert*-Butoxicarbonilpiperidin-4-iloxi)-3,4-dihidro-7-metoxiquinazolin-4-ona**

Di-*tert*-butilazodicarboxilato (915 mg) se agregó a una solución agitada de 5-hidroxi-7-metoxi-3-pivaloiloiloximetil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 12.1) (800 mg), 1-*tert*-butoxicarbonil-4-hidroxipiperidina (631 mg), y trifenilfosfina (1.02 g) en DCM seco (13 ml), bajo una atmósfera de nitrógeno. Se aplicó enfriamiento externo (baño

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helado) durante la adición. La reacción se agitó entonces durante 10 minutos, tras lo cual se la dejó calentar a temperatura ambiente. Trascurridas 2 horas, la mezcla se concentró *in vacuo* para proporcionar el material crudo como un aceite anaranjado. Una solución de amoníaco en metanol (7N) se agregó a esta mezcla cruda, para proporcionar una solución anaranjada, la cual se agitó a temperatura ambiente durante 24 horas. A continuación la mezcla se concentró *in vacuo*, y el residuo se purificó por cromatografía de columna, usando 0-10% metanol en DCM, para proporcionar el compuesto del título como una espuma blanca que se solidificó al secar durante la noche (892 mg, 91%); Espectro NMR (CDCl_3) 1.47 (s, 9H), 1.93 (m, 4 H), 3.54 (m, 2H) 3.70 (m, 2H), 3.90 (s, 3H), 4.66 (m, 1H), 6.50 (d, 1H), 6.77 (d, 1H), 7.89 (s, 1H), 10.32 (s, 1H); Espectro de masa M-H^+ 374.

Ejemplo de Referencia 16

4-Cloro-7-(3-(R)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina

Oxicloruro de fósforo (1.4 ml) se agregó a una solución de 3,4-dihidro-7-(3-(R)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14) (1.75 g) y diisopropiletilamina (6.3 ml) en 1, 2-dicloroetano (100 ml), y la solución resultante se calentó a reflujo durante 3 horas. La reacción se enfrió y se concentró *in vacuo* y el residuo se purificó por cromatografía usando DCM-metanol-trietilamina (8:1:1) como eluyente. El sólido resultante se trituró con DCM y se filtró. El filtrado se evaporó para producir el compuesto del título como un sólido amarillo (1.5 g, 81%); Espectro de masa M^+ 390.

El procedimiento descrito arriba se repitió usando la 3,4-dihidroquinazolin-4-ona apropiada. Así se obtuvo el compuesto descrito a continuación:

Ejemplo de Referencia 16.1

4-Cloro-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida de 3,4-dihidro-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 7) en 66% de rendimiento; Espectro NMR

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(CDCl₃) 2.10 (m, 2H), 2.23 (m, 2H), 2.42 (s, 3H), 2.60 (m, 2H), 2.84 (m, 2H), 4.73 (m, 1H), 7.04 (d, 1H), 7.62 (d, 1H), 7.81 (t, 1H), 8.93 (s, 1H);

Espectro de masa M⁺ 278.

Ejemplo de Referencia 16.2

4-Cloro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida de 3,4-dihidro-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.5) en 99% de rendimiento; Espectro NMR (CDCl₃) 2.10 (m, 4H), 2.35 (s, 3H), 2.44 (m, 2H), 2.74 (m, 2H), 3.95 (s, 3H), 4.58 (s, 1H), 6.60 (d, 1H), 6.94 (d, 1H), 8.80 (s, 1H); Espectro de masa MH⁺ 308.

Ejemplo de Referencia 16.3

5-(1-*tert*-Butoxicarbonilpiperidin-4-iloxi)-4-cloroquinazolina

Obtenida de 5-(1-*tert*-butoxicarbonilpiperidin-4-iloxi)-3,4-dihidroquinazolina (Ejemplo de Referencia 7.1) en 66% de rendimiento; Espectro NMR (DMSO-d₆) 1.38 (s, 9H), 1.58 -1.90 (m, 4H), 3.30 - 3.60 (m, 4H), 4.82 (m, 1H), 7.14 - 7.28 (m, 2H), 7.74 (t, 1H), 8.33 (s, 1H).

Ejemplo de Referencia 17

Clorhidrato de 4-cloro-5-fluoroquinazolina

A una suspensión de 3,4-dihidro-5-fluoroquinazolin-4-ona (0.5 g) en cloruro de tionilo (5 ml) se agregó DMF (0.2 ml). La mezcla se calentó a reflujo bajo una atmósfera de nitrógeno durante 3 horas. La mezcla se evaporó *in vacuo*, el residuo se re-suspendió en tolueno seco, y se evaporó nuevamente. El residuo se secó *in vacuo* para proporcionar el compuesto del título como un sólido amarillo pálido (634 mg, 95%), el cual se usó sin más manipulación.

Ejemplo de Referencia 18

Clorhidrato de 4-(3-cloro-4-fluoroanilino)-5-fluoroquinazolina

DMF (1 ml) se agregó gota a gota a 5-fluoro-3,4-dihidroquinazolin-4-ona (1.00 g) en cloruro de tionilo (10 ml). La reacción se calentó a 110°C durante 18 horas para proporcionar una solución anaranjada. La mezcla de reacción se concentró *in vacuo* para proporcionar un sólido anaranjado. Este sólido se agregó en porciones a un frasco que contenía hielo (100 g) y

una solución de carbonato hidrogenado de sodio acuoso saturado (50 ml), manteniendo la temperatura interna < 5 °C y comprobando que la solución permaneciera básica. A continuación la mezcla acuosa se extrajo con DCM (3 x 100 ml), se combinaron los extractos orgánicos, se secaron (MgSO₄), y se concentraron *in vacuo* para proporcionar un sólido anaranjado. Se agregaron 3-cloro-4-fluoroanilina (0.88 g) y 1N HCl en éter dietílico (6.09 ml) al sólido anaranjado suspendido en IPA (50 ml). La mezcla resultante se calentó a 100°C durante 90 minutos, luego se dejó enfriar a temperatura ambiente. El sólido se filtró y se lavó con IPA (5 ml), luego éter dietílico (20 ml) para proporcionar el compuesto del título, como un sólido beige (1.37 g, 69%): Espectro de masa MH⁺ 292.

Ejemplo de Referencia 19

7-Benciloxi-4-(3-cloro-4-fluoroanilino)-5-(tetrahidropiran-4-iloxi)quinazolina

Di-isopropiletilamina (2.27 ml) se agregó a 7-benciloxi-3,4-dihidro-5-(tetrahidropiran-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.3) (638 mg) disuelta en 1,2-dicloroetano anhidro (30 ml) y la solución resultante enfriada a 0°C en un baño helado. Se agregó gota a gota oxicloruro de fósforo (0.51 ml) y la reacción se calentó a reflujo durante 3 horas. La mezcla de reacción se concentró *in vacuo* para proporcionar un aceite anaranjado. Se agregó 3-cloro-4-fluoroanilina (99 mg) a este aceite disuelto en IPA (15 ml), seguida por di-isopropiletilamina (0.16 ml). La mezcla resultante se calentó a reflujo durante 1.5 horas. La mezcla de reacción se enfrió a temperatura ambiente, y el sólido resultante se filtró, se lavó con IPA, luego éter dietílico y se secó *in vacuo* para proporcionar el compuesto del título como un sólido verde (0.577 g, 67%); Espectro de masa MH⁺ 480.

El procedimiento descrito arriba se repitió usando la 3,4-dihidroquinazolin-4-ona y anilina apropiadas. Así se obtuvo el compuesto descrito a continuación:

Ejemplo de Referencia 19.1

4-(3-Cloro-4-fluoroanilino)-5, 7-dimetoxiquinazolina

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Obtenida de 3,4-dihidro-5,7-dimetoxiquinazolin-4-ona (Ejemplo de Referencia 5.2) y 3 cloro-4-fluoroanilina en 92% de rendimiento; Espectro NMR (DMSO-d6) 4.0 (s, 3H), 4.1 (s, 3H), 6.9-7.0 (dd, 2H), 7.5-7.6 (m, 2H), 7.9 (dd, 1H), 8.7 (s, 1H); Espectro de masa M-H⁺ 334.

Ejemplo de Referencia 19.2

7-Benciloxi-4-(3-bromoanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida de 7-benciloxi-3,4-dihidro-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.4) y 3-bromoanilina en 38% de rendimiento; Espectro de masa MH⁺ 521.

Ejemplo de Referencia 19.3

7-Benciloxi-4-(3-cloro-4-fluoroanilino)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida de 7-benciloxi-3,4-dihidro-5-(tetrahydrofurano-3-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.6) y 3-cloro-4-fluoroanilina en 34% de rendimiento; Espectro de masa MH⁺ 466.

Ejemplo de Referencia 19.4

7-Benciloxi-4-(3-cloro-4-fluoroanilino)-5-ciclopentiloxiquinazolina

Obtenida de 7-benciloxi-5-ciclopentiloxi-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 14.7) y 3-cloro-4-fluoroanilina en 47% de rendimiento; Espectro NMR (DMSO-d6) 1.72 (m, 4H), 2.02 (m, 4H), 5.29 (m, 1H), 5.32 (s, 2H), 7.01 (d, 1H), 7.07 (d, 1H), 7.39 (m, 3H) 7.53 (m, 4H), 8.06 (m, 1H), 8.81 (s, 1H), 10.42 (bs, 1H); Espectro de masa MH⁺ 464.

Ejemplo de Referencia 19.5

7-Benciloxi-4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida de 7-benciloxi-3,4-dihidro-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.4) y 3-cloro-4-fluoroanilina en 21% de rendimiento; Espectro NMR (DMSO-d6) 2.3 (m, 2H), 2.4 (m, 1H), 2.7 (d, 3H), 3.2 (m, 2H), 3.3 (m, 1H), 3.5 (m, 2H), 5.1 (m, 1H), 5.3 (s, 2H), 7.1 (s, 2H), 7.4 (m, 3H), 7.5 (m, 3H), 7.6 (m, 1H), 8.0 (m, 1H), 8.8 (d, 1H); Espectro de masa MH⁺ 493.

Ejemplo de Referencia 19.6

**7-Bencil xi-4-(3-metilanilin)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenida de 7-benciloxi-3,4-dihidro-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.4) y 3-metilanilina en 32% de rendimiento; Espectro NMR (DMSO-d6) 2.2 (m, 2H), 2.4 - 2.5 (m, 6H), 2.7 (m, 2H), 3.1 (m, 2H), 3.5 (m, 2H), 5.1 (m, 1H), 5.3 (s, 2H), 7.1 - 7.2 (m, 2H), 7.3 - 7.6 (m, 8H), 8.0 (m, 1H), 8.8 (m, 1H); Espectro de masa MH⁺ 455.

Ejemplo de Referencia 19.7**7-Benciloxi-4-(3-cloroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenida de 7-benciloxi-3,4-dihidro-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.4) y 3-cloroanilina en 26% de rendimiento; Espectro NMR (DMSO-d6) 2.2(m, 2H), 2.3 - 2.4 (m, 5H), 2.7 (m, 2H), 3.1 (m, 2H), 3.4 (m, 2H), 5.1 (m, 1H), 5.3 (s, 2H), 7.0 - 7.2 (m, 3H), 7.3 - 7.6 (m, 8H), 8.8 (m, 1H); Espectro de masa MH⁺ 475.

Ejemplo de Referencia 19.8**7-Benciloxi-4-(3-cloro-4-(3-fluorobenciloxi)anilina)-5-ciclopentiloxiquinazolina**

Obtenida de 7-benciloxi-5-ciclopentil-3,4-dihidroquinazolin-4-ona (Ejemplo de Referencia 14.7) y 3-cloro-4-(3-fluorobenciloxi)anilina (Ejemplo de Referencia 28) en 62% de rendimiento; Espectro de masa MH⁺ 570.

Ejemplo de Referencia 19.9**7-Benciloxi-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenida haciendo reaccionar 7-benciloxi-3,4-dihidro-5-(1-metilpiperidin-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.4) y 3-cloro-4-(3-fluorobenciloxi)anilina (Ejemplo de Referencia 28) en 96% de rendimiento; Espectro de masa MH⁺ 599.

Ejemplo de Referencia 19.10**7-Benciloxi-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)quinazolina**

Obtenida haciendo reaccionar 7-benciloxi-3,4-dihidro-5-(tetrahidropiran-4-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.3) con 3-cloro-4-(3-fluorobenciloxi)anilina (Ejemplo de Referencia 28) en 70% de rendimiento; Espectro de masa MH^+ 585.

Ejemplo de Referencia 19.11

7-Benciloxi-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidrofurano-3-iloxi)quinazolina

Obtenida haciendo reaccionar 7-benciloxi-3,4-dihidro-5-(tetrahidrofurano-3-iloxi)quinazolin-4-ona (Ejemplo de Referencia 14.3) con 3-cloro-4-(3-fluorobenciloxi)anilina (Ejemplo de Referencia 28) en 70% de rendimiento; Espectro NMR (DMSO- d_6) 2.2 (m, 1H), 2.3 (m, 1H), 3.8 - 4.0 (m, 3H), 4.2 (d, 1H), 5.2 (s, 2H), 5.2 (s, 2H), 5.5 (m, 1H), 6.9 (d, 1H), 6.9 (d, 1H), 7.1 - 7.5 (m, 11H), 8.2 (d, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Espectro de masa MH^+ 572.

Ejemplo de Referencia 20

Trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(tetrahidropiran-4-iloxi)quinazolina

Una mezcla de 7-benciloxi-4-(3-cloro-4-fluoroanilino)-5-(tetrahidropiran-4-iloxi)quinazolina (Ejemplo de Referencia 19) (0.58 g) y ácido trifluoroacético (25 ml) se calentó a 70°C durante 20 horas. La mezcla de reacción se enfrió, se concentró *in vacuo*, y el residuo se trituró con éter dietílico para proporcionar el compuesto del título como un sólido verde pálido (0.49 g, 82%); Espectro NMR (DMSO- d_6) 1.94 (m, 2H), 2.15 (m, 2H), 3.53 (t, 2H), 3.89 (m, 2H), 4.96 (m, 1H), 6.81 (s, 1H), 6.92 (s, 1H), 7.50 (t, 1H), 7.57 (m, 1H), 8.09 (dd, 1H), 8.68 (s, 1H), 10.31 (s, 1H). Espectro de masa MH^+ 390.

El procedimiento descrito arriba se repitió usando la 7-benciloxiquinazolina apropiada. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 20.1

Trifluoroacetato de 4-(3-bromoanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina

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Obtenido de 7-benciloxi-4-(3-bromoanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 19.2) en 93% de rendimiento; Espectro de masa MH^+ 431.

Ejemplo de Referencia 20.2

Trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenido de 7-benciloxi-4-(3-cloro-4-fluoroanilino)-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 19.3) en 79% de rendimiento; Espectro de masa MH^+ 376.

Ejemplo de Referencia 20.3

Trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-5-ciclopentiloxi-7-hidroxiquinazolina

Obtenido de 7-benciloxi-4-(3-cloro-4-fluoroanilino)-5-ciclopentiloxiquinazolina (Ejemplo de Referencia 19.4) en 60% de rendimiento; Espectro NMR (DMSO- d_6) 1.71 (m, 4H), 2.04 (m, 4H), 5.18 (m, 1H), 6.71 (d, 1H), 6.78 (d, 1H), 7.53 (m, 2H), 8.07 (m, 1H), 8.73 (s, 1H), 10.33 (bs, 1H); Espectro de masa MH^+ 374.

Ejemplo de Referencia 20.4

Trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido de 7-benciloxi-4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 19.5) en 93% de rendimiento; Espectro de masa MH^+ 403.

Ejemplo de Referencia 20.5

Trifluoroacetato de 7-hidroxi-4-(3-metilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido de 7-benciloxi-4-(3-metilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 19.6) en 80% de rendimiento; Espectro de masa $M-H^+$ 363.

Ejemplo de Referencia 20.6

Trifluoroacetato de 4-(3-Cloroanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido de 7-benciloxi-4-(3-cloroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 19.7) en 100% de rendimiento; Espectro de masa $M-H^+$ 383.

Ejemplo de Referencia 20.7

Trifluoroacetato de 4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-5-ciclopentiloxi-7-hidroxiquinazolina

Obtenido de 7-benciloxi-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-ciclopentiloxiquinazolina (Ejemplo de Referencia 19.8) en 43% de rendimiento; Espectro de masa MH^+ 480.

Ejemplo de Referencia 20.8

Trifluoroacetato de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenido de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(1-metilpiperidin-4-iloxi)-7-benciloxiquinazolina (Ejemplo de Referencia 19.9) en 27% de rendimiento; Espectro de masa MH^+ 509.

Ejemplo de Referencia 20.9

Trifluoroacetato de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-hidroxi-5-(tetrahidropiran-4-iloxi)quinazolina

Obtenido de 7-benciloxi-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)quinazolina (Ejemplo de Referencia 19.10) en 30% de rendimiento; Espectro de masa MH^+ 496.

Ejemplo de Referencia 20.10

Trifluoroacetato de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-hidroxi-5-(tetrahidrofurano-3-iloxi)quinazolina

Obtenido de 7-benciloxi-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 19.11) en > 100% de rendimiento; Espectro de masa MH^+ 482.

Ejemplo de Referencia 21

4-(3-Cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina

Carbonato de potasio (0.21 g) y 1-bromo-3-cloropropano (40 μ l) se agregaron a una suspensión de trifluoroacetato de 4-(3-cloro-4-

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fluoroanilino)-7-hidroxi-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 20.2) (0.19 g) en DMF (4 ml). La mezcla se agitó a temperatura ambiente durante 23 horas, luego se agregó más 1-bromo-3-cloropropano (19 μ l) y la mezcla se agitó a temperatura ambiente durante 18 horas más. Seguidamente la mezcla se concentró *in vacuo*, el residuo se enfrió y se agregó agua fría. El sólido resultante se filtró, se lavó con agua fría y se secó *in vacuo* para proporcionar el compuesto del título como un sólido verde (0.15g, 88%); Espectro NMR (DMSO- d_6) 2.22 (m, 4H), 3.85 (m, 5H), 4.22 (m, 3H), 5.46 (m, 1H), 6.80 (d, 1H), 6.83 (d, 1H), 7.42 (t, 1H), 7.59 (m, 1H), 8.27 (m, 1H), 8.49 (s, 1H), 9.91 (s, 1H); Espectro de masa MH^+ 452.

El procedimiento descrito arriba se repitió usando la 7-hidroxiquinazolina y el halogenuro de alquilo apropiados. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 21.1

4-(3-Cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-ciclopentiloxiquinazolina

Obtenida de trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-5-ciclopentiloxi-7-hidroxiquinazolina (Ejemplo de Referencia 20.3) y 1-bromo-3-cloropropano en 99% de rendimiento; Espectro NMR (DMSO- d_6) 1.72 (m, 4H), 2.01 (m, 4H), 2.22 (m, 2H), 3.81 (t, 2H), 4.23 (t, 2H), 5.17 (m, 1H), 6.70 (m, 1H), 6.79 (m, 1H), 7.44 (m, 2H), 8.25 (m, 1H), 8.47 (s, 1H), 9.88 (s, 1H); Espectro de masa MH^+ 450.

Ejemplo de Referencia 21.2

4-(3-Cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida de trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 20.4) y 1-bromo-3-cloropropano en 66% de rendimiento; Espectro de masa MH^+ 479.

Ejemplo de Referencia 21.3

4-(3-Cloro-4-fluoroanilino)-7-(3-cloropropoxi)-5-(tetrahidropiran-4-iloxi)quinazolina

Obtenida de trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(tetrahidropiran-4-iloxi)quinazolina (Ejemplo de Referencia 20) y 1-bromo-3-cloropropano en 77% de rendimiento; Espectro de masa MH^+ 467.

Ejemplo de Referencia 21.4

4-(3-Cloro-4-fluoroanilino)-7-(2-cloroetoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina

Obtenida de trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(tetrahidrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 20.2) y 1-bromo-2-cloroetano en 90% de rendimiento; Espectro NMR (DMSO- d_6) 2.17 (m, 1H), 2.32 (m, 1H), 3.78 - 4.01 (m, 5H), 4.18 (d, 1H), 4.42 (t, 2H), 5.50 (m, 1H), 6.84 (m, 2H), 7.42 (t, 1H), 7.61 (m, 1H), 8.28 (m, 1H), 8.50 (s, 1H), 9.92 (s, 1H); Espectro de masa MH^+ 438.

Ejemplo de Referencia 21.5

7-(2-Cloroetoxi)-4-(3-cloro-4-fluoroanilino)-5-ciclopentiloxiquinazolina

Obtenida de trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-5-ciclopentiloxi-7-hidroxiquinazolina (Ejemplo de Referencia 20.3) y 1-bromo-2-cloroetano en 75% de rendimiento; Espectro NMR (DMSO- d_6) 1.72 (m, 4H), 2.01 (m, 4H), 3.99 (m, 2H), 4.41 (m, 2H), 5.21 (m, 1H), 6.72 (m, 1H), 6.81 (m, 1H), 7.45 (m, 2H), 8.25 (m, 1H), 8.48 (s, 1H), 9.88 (s, 1H); Espectro de masa MH^+ 436.

Ejemplo de Referencia 21.6

7-(2-Cloroetoxi)-4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida de trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 20.4) y 1-bromo-2-cloroetano en 53% de rendimiento; Espectro de masa MH^+ 465.

Ejemplo de Referencia 21.7

7-(2-Cloroetoxi)-4-(3-cloro-4-fluoroanilino)-5-(tetrahidropiran-4-iloxi)quinazolina

Obtenida de trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(tetrahidropiran-4-iloxi)quinazolina (Ejemplo de Referencia 20) y 1-bromo-2-cloroetano en 85% de rendimiento; Espectro de masa MH^+ 452.

Ejemplo de Referencia 21.8**4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(3-cloropropoxi)-5-ciclopentiloxiquinazolina**

Obtenida de trifluoroacetato de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-ciclopentiloxi-7-hidroxiquinazolina (Ejemplo de Referencia 20.7) y 1-bromo-3-cloropropano en 100% de rendimiento; Espectro NMR (DMSO-d₆) 1.60 -1.82 (m, 4H), 1.90 - 2.15 (m, 4H), 2.22 (m, 2H), 3.82 (t, 2H), 4.23 (t, 2H), 5.18 (m, 1H), 5.23 (s, 2H), 6.68 (d, 1H), 6.78 (d, 1H), 7.17 (m, 1H), 7.25 (m, 3H), 7.43 (m, 2H), 8.13 (d, 1H), 8.42 (s, 1H), 9.80 (s, 1H); Espectro de masa MH⁺ 556.

Ejemplo de Referencia 21.9**7-(2-Cloroetoxi)-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-ciclopentiloxiquinazolina**

Obtenida de trifluoroacetato de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-ciclopentiloxi-7-hidroxiquinazolina (Ejemplo de Referencia 20.7) y 1-bromo-2-cloroetano en 100% de rendimiento; Espectro de masa MH⁺ 542.

Ejemplo de Referencia 21.10**4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(3-cloropropoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Obtenida de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 20.8) y 1-bromo-3-cloropropano en 78% de rendimiento; Espectro de masa MH⁺ 585.

Ejemplo de Referencia 21.11**7-(2-Cloroetoxi)-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)quinazolina**

Obtenida de 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-hidroxi-5-(tetrahidropiran-4-iloxi)quinazolina (Ejemplo de Referencia 20.9) y 1-bromo-2-cloroetano en 83% de rendimiento; Espectro de masa MH⁺ 558.

Ejemplo de Referencia 21.12**4-(3-Cloro-4-(3-fluorobencil ox i)anilin)-7-(3-cloropropoxi)-5-**

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(tetrahidropiran-4-il xi)quinazolina

Obtenida haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-hidroxiquinazolina (Ejemplo de Referencia 20.9) y 1-bromo-3-cloropropano en 100% de rendimiento; Espectro NMR (CDCl₃) 2.0 (m, 2H), 2.3 (m, 4H), 2.8 (t, 4H), 3.6 (m, 2H), 3.8 (t, 2H), 4.1 (dt, 2H), 4.2 (t, 2H), 4.8 (m, 1H) 5.2 (s, 2H), 6.5 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H), 7.0 (m, 1H), 7.2 (m, 2H), 7.4 (m, 1H), 7.5 (dd, 1H), 7.9 (d, 1H), 8.5 (s, 1H), 9.7 (s, 1H); Espectro de masa MH⁺ 572.

Ejemplo de Referencia 21.13**4-(3-Cloro-4-(3-fluorobenciloxi)anilino)-7-(3-cloropropoxi)-5-(tetrahidrofurano-3-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-hidroxiquinazolina (Ejemplo de Referencia 20.10) y 1-bromo-3-cloropropano en 91% de rendimiento; Espectro NMR (DMSO-d₆) 2.1 - 2.4 (m, 4H), 3.8 - 4.0 (m, 5H), 4.2 - 4.3 (m, 3H), 5.2 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.1 - 7.3 (m, 4H), 7.4 - 7.5 (m, 2H), 8.2 (d, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Espectro de masa MH⁺ 558.

Ejemplo de Referencia 21.14**7-(2-Cloroetoxi)-4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidrofurano-3-iloxi)quinazolina**

Obtenido haciendo reaccionar 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-5-(tetrahidropiran-4-iloxi)-7-hidroxiquinazolina (Ejemplo de Referencia 20.10) y 1-bromo-2-cloroetano en 100% de rendimiento; Espectro NMR (DMSO-d₆) 2.2 (m, 1H), 2.3 (m, 1H), 3.8 - 4.0 (m, 5H), 4.2 (d, 1H), 4.4 (t, 2H), 5.2 (s, 2H), 5.5 (m, 1H), 6.8 (m, 2H), 7.1 - 7.3 (m, 4H), 7.4 - 7.5 (m, 2H), 8.2 (m, 1H), 8.5 (s, 1H), 9.8 (s, 1H); Espectro de masa MH⁺ 544.

Ejemplo de Referencia 22**7-(1-tert-Butoxicarbonilpiperidin-4-ilmetoxi)-4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina**

Carbonato de potasio (240 mg) se agregó a trifluoroacetato de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 20.4) (175 mg) en DMA (5 ml). Se agregó 1-(*tert*-butoxicarbonil)-4-tosiloximetilpiperidina (Ejemplo de Referencia 41) (161 mg) y la mezcla resultante se agitó durante 18 horas a temperatura ambiente. La reacción se calentó entonces a 60°C durante 18 horas y el solvente se concentró *in vacuo* para proporcionar un sólido. A esto se agregó agua y se filtró el sólido para proporcionar el compuesto del título como un sólido beige (100 mg, 38%); Espectro NMR (DMSO-d6) 1.2 (m, 2H), 1.4 (s, 9H), 1.5 (m, 1H), 1.7 (m, 2H), 1.9 (m, 2H), 2.1 (m, 2H), 2.2 (s, 3H), 2.2 (m, 2H), 3.8 (m, 2H), 4.0 (m, 4H), 4.8 (m, 1H), 6.8 (s, 2H), 7.4 (m, 2H), 7.6 (m, 1H), 7.8 (d, 1H), 8.2 (dd, 1H), 8.5 (s, 1H), 9.9 (s, 1H); Espectro de masa MH⁺ 600.

El procedimiento descrito arriba se repitió usando la 7-hidroxiquinazolina apropiada. Así se obtuvo el compuesto descrito a continuación:

Ejemplo de Referencia 22.1

7-(1-*tert*-Butoxicarbonilpiperidin-4-ilmetoxi)-4-(3-cloroanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina

Obtenida de trifluoroacetato de 4-(3-cloroanilino)-7-hidroxi-5-(1-metilpiperidin-4-iloxi)quinazolina (Ejemplo de Referencia 20.6) en 35% de rendimiento; Espectro de masa MH⁺ 582.

Ejemplo de Referencia 22.2

7-(1-*tert*-Butoxicarbonilpiperidin-4-ilmetoxi)-4-(3-cloro-4-fluoroanilino)-5-(tetrahydrofurano-3-iloxi)quinazolina

Obtenida de 4-(3-cloro-4-fluoroanilino)-7-hidroxi-5-(tetrahydrofurano-3-iloxi)quinazolina (Ejemplo de Referencia 20.2) en 86% de rendimiento; Espectro de masa MH⁺ 574.

Ejemplo de Referencia 23

N-*tert*-Butoxicarbonil-3,5-dibenciloxianilina

Di-*isopropiletilamina* (6 ml) y en azida de difenilfosforilo (7 ml) se agregaron a una suspensión de ácido 3,5-dibenciloxibenzoico (10 g) en *tert*-

butanol (150 ml), y la reacción se agitó a 70°C durante 5 horas. La reacción se enfrió, se concentró *in vacuo* y el residuo se purificó por cromatografía (isohexano-5% acetato de etilo) para proporcionar el compuesto del título como un sólido blanco (5.8 g, 48%); Espectro NMR (DMSO-d₆) 1.43 (s, 9H), 5.00 (s, 4H), 6.30 (s, 1H), 6.80 (s, 1H), 7.10 - 7.42 (m, 10H), 9.24 (s, 1H); Espectro de masa M-H⁺ 404.

Ejemplo de Referencia 24

Trifluoroacetato de 3,5-dibenciloxianilina

Ácido trifluoroacético (20 ml) se agregó a una solución de 3,5-dibenciloxi-*N-tert*-butoxicarbonilanilina (Ejemplo de Referencia 23) (5.75 g) en DCM (150 ml) y la reacción se agitó durante 4 horas. La reacción se concentró *in vacuo* para producir el compuesto del título como un sólido beige (7.4 g, >100%); Espectro de masa MH⁺ 306. Alternativamente, el producto pudo aislarse como la sal clorhidrato dividiendo en partes entre bicarbonato de sodio acuoso saturado y acetato de etilo, y acidificación de los extractos orgánicos por adición de una solución 1M HCl en éter.

Ejemplo de Referencia 25

5-Amino-3-bromoindazol

Tricloruro de titanio (10% solución en HCl, 45 ml) se agregó gota a gota a una solución de acetato de amonio (6.36 g) y 3-bromo-5-nitroindazol (obtenido como se describe en *Eur. J. Med. Chem.*, (1986), 21(4), 359-362) (1.0 g) en una mezcla de acetona (60 ml) y agua (10 ml). La mezcla se agitó a temperatura ambiente durante 30 minutos antes de verter en agua (150 ml) y neutralizar con 10N hidróxido de sodio. La mezcla acuosa se extrajo entonces con acetato de etilo (3 x 100 ml), los extractos orgánicos se lavaron con salmuera saturada, luego se combinaron, se secaron y se concentraron *in vacuo* para proporcionar el compuesto del título como un sólido rosado pálido (0.76 g, 86%); Espectro NMR (DMSO-d₆) 5.12 (bs, 2H), 6.54 (s, 1H), 6.83 (d, 1H), 6.86 (d, 1H), 12.88 (bs, 1H); Espectro de masa MH⁺ 212.

El procedimiento descrito arriba se repitió usando el compuesto nitro arilo apropiado. Así se obtuvieron los compuestos descritos a continuación:

Ejempl de Referencia 25.1**5-Amino-3-cloroindazol**

Obtenido de 3-cloro-5-nitroindazol en 87% de rendimiento; Espectro NMR (DMSO-d₆) 4.99 (bs, 2H), 6.58 (m, 1H), 6.83 (d, 1H), 6.86 (d, 1H), 12.71 (bs, 1H).

Ejemplo de Referencia 25.2**5-Amino-3-bromoindol**

Obtenido de 3-bromo-5-nitroindol (Ejemplo de Referencia 30.1) en 80% de rendimiento; Espectro NMR (DMSO-d₆) 5.48 (bs, 2H), 6.61 (m, 2H), 7.15 (d, 1H), 7.32 (d, 2H), 10.99 (s, 1H); Espectro de masa MH⁺ 211.

Ejemplo de Referencia 26**5-Amino-3-cloro-1-(2-piridilmetil)indol**

Una solución de 3-cloro-5-nitro-1-(2-piridilmetil)indole (Ejemplo de Referencia 33) (2.5 g) en etanol (130 ml) se agitó a temperatura ambiente. Se agregó ditionito de sodio (7.6 g) en agua (18 ml), y la mezcla se calentó a 50°C durante 5 horas, luego se enfrió a temperatura ambiente. El etanol se retiró *in vacuo*, y el residuo se dividió en porciones entre DCM y agua. Se separó la capa DCM, se secó sobre sulfato de sodio, luego se concentró *in vacuo* para proporcionar el material crudo, el cual se purificó por cromatografía usando 50% DCM en isohexano, a continuación DCM como eluyente para proporcionar el compuesto del título como un sólido anaranjado (488 mg, 23%); Espectro NMR (CDCl₃) 3.53 (s, 2H), 5.27 (s, 2H), 6.61 (dd, 1H), 6.68 (d, 1H), 6.86 (d, 1H), 7.01 (d, 1H), 7.04 (s, 1H), 7.11 (dd, 1H), 7.47 (dt, 1H), 8.55 (m, 1H); Espectro de masa MH⁺ 258.

El procedimiento descrito arriba se repitió usando el compuesto nitro arilo apropiado. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 26.1**5-Amino-3-cloro-1-(2-piridilmetil)indazol**

Obtenido de 3-cloro-5-nitro-1-(2-piridilmetil)indazol (Ejemplo de Referencia 33.1) en 24% de rendimiento; Espectro NMR (CDCl₃) 3.3 (bs, 2H), 6.65 (dd, 1H), 6.77 (m, 1H), 6.84 -7.02 (m, 5H), 7.24 (m, 1H).

Ejemplo de Referencia 26.2

**5-Amino-3-cloroindol**

Obtenido de 3-cloro-5-nitroindol (Ejemplo de Referencia 30) en 17% de rendimiento; Espectro NMR (DMSO-d6) 4.7 - 4.9 (bs, 2H), 6.6 (m, 2H), 7.1 (d, 1H), 7.2 (d, 1H).

Ejemplo de Referencia 26.3**3-Fluoro-4-(1-metil-1H-imidazol-2-iltio)anilina**

Obtenida de 3-fluoro-4-(1-metil-1H-imidazol-2-iltio)nitrobencono (Ejemplo de Referencia 43) en 86% de rendimiento; Espectro de masa MH⁺ 224.

Ejemplo de Referencia 27**5-Amino-3-metilbenzisotiazol**

3-Metil-5-nitrobenzisotiazol (1 g) y 10% Pd/C (0.3 g) en etanol (40 ml) se agitaron durante 16 horas bajo una atmósfera de hidrógeno. Los residuos sólidos se retiraron por filtración y la solución se concentró *in vacuo*. El residuo se trituró con éter y se filtró para proporcionar el compuesto del título como un sólido amarillo pálido (0.25 g, 30% de rendimiento); Espectro NMR (DMSO-d6) 2.52 (s, 3H), 5.30 (bs, 2H), 6.95 (dd, 1H), 7.03 (dd, 1H), 7.70 (d, 1H).

El procedimiento descrito arriba se repitió usando el compuesto nitro apropiado. Así se obtuvo el compuesto descrito a continuación: **Ejemplo de Referencia 27.1**

5-Amino-3-metilindol

Obtenido de 3-metil-5-nitroindol (Ejemplo de Referencia 31) en 66% de rendimiento; Espectro NMR (DMSO-d6) 2.1 (s, 3H), 4.4 (bs, 2H), 6.4 (dd, 1H), 6.6 (d, 1H), 6.8 (d, 1H), 7.0 (d, 1H); Espectro de masa MH⁺ 147.

Ejemplo de Referencia 27.2**5-Aminoindole-3-carbonitrilo**

Obtenido de 5-nitroindol-3-carbonitrilo (Ejemplo de Referencia 38) en 71% de rendimiento; Espectro NMR (DMSO-d6) 4.8 (bs, 2H), 6.6 (dd, 1H), 6.7 (s, 1H), 7.2 (d, 1H), 7.9 (s, 1H); Espectro de masa MH⁺ 158.

Ejemplo de Referencia 28

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3-Cloro-4-(3-fluorobenciloxi)anilina

A una solución de 2-cloro-1-(3-fluorobenciloxi)-4-nitrobenceno (Ejemplo de Referencia 34) (3.74 g) en acetato de etilo (60 ml) se agregó 10% Pt/C (0.5 g). La solución resultante se sometió a una atmósfera de nitrógeno durante 4 horas a temperatura ambiente. Seguidamente el catalizador se extrajo por filtración y el solvente se concentró *in vacuo* para proporcionar el compuesto del título como un sólido cristalino anaranjado (3.08 g, 92%); Espectro NMR (DMSO-d₆) 4.91 (s, 2H), 5.01 (s, 2H), 6.45 (dd, 1H), 6.63 (s, 1H), 6.89 (d, 1H), 7.12 (t, 1H), 7.24 (t, 2H), 7.40 (m, 1H); Espectro de masa MH⁺ 252.

Ejemplo de Referencia 29**4-(Azepan-1-ilcarbonil)-3-cloroanilina**

A 1-(2-cloro-4-nitrobenzoil)azepán (Ejemplo de Referencia 37) (2.58 g) se agregó acetato de etilo; (100 ml) y dihidrato de cloruro de estaño (II) (9 g). Este se calentó a 70°C durante 4 horas, luego se dejó enfriar. La mezcla se hizo básica con 880 solución de amoníaco, el sólido resultante se filtró. El filtrado se extrajo con agua y los extractos combinados se secaron y se concentraron *in vacuo*. El residuo se purificó por cromatografía usando DCM - 30% acetato de etilo como eluyente para proporcionar el compuesto del título como un sólido blanco (1.85 g, 73%); Espectro NMR (CDCl₃) 1.48 -1.74 (m, 6H), 1.74 -1.92 (m, 2H), 3.23 - 3.33 (m, 2H), 3.35 - 3.84 (m, 2H), 3.85 (s, 2H), 6.54 (dd, 1H), 6.68 (d, 1H), 7.02 (d, 1H); Espectro de masa MH⁺ 253.

Ejemplo de Referencia 30**3-Cloro-5-nitroindol**

N-Clorosuccinimida (1.65 g) se agregó en porciones a una solución de 5-nitroindol (2.00 g) en DMF (20 ml). La solución resultante se agitó a temperatura ambiente durante 18 horas. La solución marrón pálida se vertió en agua (200 ml) para proporcionar un precipitado amarillo, el cual se filtró, se lavó con agua y se secó *in vacuo* para proporcionar el compuesto del título como un sólido amarillo (2.40 g, 99%). Espectro de masa M-H⁺ 195.

El procedimiento descrito arriba se repitió usando la *N*-halosuccinimida apropiada. Así se obtuvo el compuesto descrito a continuación:

Ejemplo de Referencia 30.1

3-Bromo-5-nitroindol

Obtenida de *N*-bromosuccinimida en 89% de rendimiento; Espectro NMR (DMSO-*d*₆) 7.60 (d, 1H), 7.82 (d, 1H), 8.04 (dd, 1H), 8.30 (d, 1H), 12.16 (bs, 1H).

Ejemplo de Referencia 31

3-Metil-5-nitroindol

Bromuro de tetra-*n*-butilamonio (1.25 g) y trietilamina (1.37 ml) se agregaron a alil-(2-bromo-4-nitrofenil)amina (**Ejemplo de Referencia 32**) (1.00 g) disuelta en DMF (5 ml). Se agregó acetato de paladio (II) y la reacción se agitó a temperatura ambiente durante 72 horas. La reacción se filtró a través de celita luego de la dilución con acetato de etilo. La solución se lavó con agua (50 ml), 5% HCl acuoso (50 ml), salmuera (50 ml) y se secó. La concentración *in vacuo* produjo un sólido marrón, el cual se purificó por cromatografía usando DCM como eluyente para proporcionar el compuesto del título como un sólido amarillo (680 mg, 99%); Espectro NMR (DMSO-*d*₆) 2.3 (s, 3H), 7.4 (d, 1H), 7.5 (d, 1H), 8.0 (dd, 1H), 8.5 (d, 1H); Espectro de masa M-H⁺ 175.

Ejemplo de Referencia 32

Alil-(2-bromo-4-nitrofenil)amina

Tert-butóxido de potasio (2.71 g) se agregó a 2-bromo-4-nitroanilina (5.00g) en DMF (30 ml) a 0°C. La solución roja resultante se agitó a esta temperatura durante 30 minutos. Se agregó bromuro de alilo (2.05 ml) gota a gota y la mezcla de reacción se agitó durante 18 horas a temperatura ambiente. La mezcla de reacción se vertió en 20% NaH₂PO₄ y se extrajo con acetato de etilo. Se secaron los extractos orgánicos combinados, se filtraron y se concentraron *in vacuo* para proporcionar un aceite anaranjado. Éste se purificó por cromatografía usando acetato de etilo / isohexano (1:9) como eluyente para proporcionar el compuesto del título como un sólido cristalino amarillo (2.25 g, 38%); Espectro NMR (DMSO-*d*₆) 4.0 (m, 2H),

5.1 (d, 1H), 5.2 (dd, 1H), 5.9 (m, 1H), 6.7 (d, 1H), 6.9 (t, 1H), 8.0 (dd, 1H), 8.3 (d, 1H).

Ejemplo de Referencia 33

3-Cloro-5-nitro-1-(2-piridilmetil)indol

Clorhidrato de cloruro de 2-picolilo (3.26 g) se agregó a una mezcla agitada de 3-cloro-5-nitroindol (**Ejemplo de Referencia 30**) (1.97 g) y carbonato de potasio (13.8 g) en DMF (50 ml). La mezcla se calentó a 50°C y se agitó durante 2 horas, tiempo después del cual se retiró el solvente *in vacuo*. El residuo se disolvió en DCM, luego se lavó con agua, y se secó sobre sulfato de sodio. La concentración proporcionó el producto como un sólido amarillo (2.53 g, 88%); **Espectro NMR** (CDCl₃) 5.43 (s, 2H), 6.90 (d, 1H), 7.23 (dd, 1H), 7.35 (s, 1H), 7.37 (d, 1H), 7.62 (dt, 1H), 8.12 (dd, 1H), 8.60 (m, 2H).

El procedimiento descrito arriba se repitió usando el heterociclo y el halogenuro de alquilo apropiados. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 33.1

3-Cloro-5-nitro-1-(2-piridinilmetil)indazol

Obtenido de 3-cloro-5-nitroindazole y clorhidrato de cloruro de 2-picolilo en 74% de rendimiento; **Espectro NMR** (CDCl₃) 5.32 (s, 2H), 6.80 (d, 1H), 6.89 (d, 1H), 7.01 (dt, 1H), 7.28 (m, 3H), 8.12 (dd, 1H), 8.61 (d, 1H).

Ejemplo de Referencia 34

2-Cloro-1-(3-fluorobenciloxi)-4-nitrobenceno

A una solución de 2-cloro-4-nitrofenol (20.0 g) en acetona (400 ml) se agregó carbonato de potasio (47.76 g) seguido por la adición gota a gota de bromuro de 3-fluorobencilo (32.67 g) durante 15 minutos. La mezcla de reacción se agitó entonces a temperatura ambiente durante 16 horas y se filtró para retirar el material insoluble. A continuación el solvente se concentró *in vacuo* y el sólido remanente se purificó por cromatografía usando 30-80% DCM / isohexano como eluyente para proporcionar el compuesto del título (30.96 g, 95%); **Espectro NMR** (DMSO-d⁶) 5.39 (s,

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2H), 7.18 (t, 1H), 7.30 (m, 2H), 7.45 (m, 2H), 8.23 (dd, 1H), 8.32 (d, 1H); Espectro de masa M-H⁺ 280.

El procedimiento descrito arriba se repitió usando el fenol y el halogenuro de alquilo apropiados. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 34.1

4-(2-Fluorobenciloxi)-3-iodonitrobenceno

Obtenido de bromuro de 2-fluorobencilo y 4-hidroxi-3-iodonitrobenceno en 85% de rendimiento; Espectro de masa M-H⁺ 372.

Ejemplo de Referencia 34.2

4-(3-Fluorobenciloxi)-3-iodonitrobenceno

Obtenido haciendo reaccionar 4-hidroxi-3-iodonitrobenceno y bromuro de 3-fluorobencilo en 99% de rendimiento; Espectro de masa M-H⁺ 372.

Ejemplo de Referencia 35

4-(2-Fluorobenciloxi)-3-(trimetilsililetinil)nitrobenceno

A una solución de 4-(2-fluorobenciloxi)-3-yodonitrobenceno (0.49 g) (Ejemplo de Referencia 34.1) en acetonitrilo (10 ml) se agregó trimetilsililacetileno (0.54 ml), yoduro de cobre(I) (5 mg), bis(trifenilfosfina)-dicloropaladio (18 mg) y trietilamina (10 ml) bajo nitrógeno y la mezcla se agitó a temperatura ambiente durante 4 horas. La reacción se concentró *in vacuo* y el residuo se purificó por cromatografía usando DCM como eluyente para proporcionar el compuesto del título como un sólido amarillo (0.33 g, 73%); Espectro de masa M-H⁺ 342.

El procedimiento descrito arriba se repitió usando el halobenceno apropiado. Así se obtuvieron los compuestos descritos a continuación:

Ejemplo de Referencia 35.1

4-(3-Fluorobenciloxi)-3-(trimetilsililetinil)nitrobenceno

Obtenido de 4-(3-fluorobenciloxi)-3-yodonitrobenceno (Ejemplo de Referencia 34.2); Espectro de masa M-H⁺ 342.

Ejemplo de Referencia 36

4-Hidroxitetrahidrotiopirano

Borohidruro de sodio (60 mg) se agregó a 2M NaOH (100 μ l) y la solución resultante se diluyó con agua (0.75 ml). Esta solución se agregó gota a gota a tetrahidrotiopiran-4-ona (0.5 g) en metanol (5 ml) usando un baño helado para mantener la temperatura interna a 18-25°C. Se agregaron otros 0.13 equivalentes de borohidruro de sodio y, después de agitar a temperatura ambiente durante 30 minutos, la reacción se concentró *in vacuo* a un volumen mínimo y se agregó agua (5 ml). La solución se extrajo con éter dietílico (6 x 20ml), se secó y se concentró *in vacuo* para proporcionar el compuesto del título como un aceite incoloro (0.48 g, 94%); Espectro NMR (DMSO-d₆) 1.5 (m, 2H), 2.0 (m, 2H), 2.4 (m, 2H), 2.7 (m, 2H), 3.4 (m, 1H), 4.6 (d, 1H).

Ejemplo de Referencia 37

1-(2-Cloro-4-nitrobenzoil)azepán

A una solución de ácido 2-cloro-5-nitrobenzoico (4.02 g) y trietilamina (2.20 g) en DCM (150 ml) se agregó hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (8.36 g). Esta mezcla se agitó a temperatura ambiente bajo una atmósfera de nitrógeno durante 3 horas. Hexametenimina (2.18 g) se agregó y esta mezcla se agitó a temperatura ambiente durante 2 horas. El solvente se retiró *in vacuo* y el residuo se purificó por cromatografía usando 0-10% acetato de etilo en DCM como eluyente para proporcionar el compuesto del título como un aceite incoloro que cristalizó al reposar (5.09 g, 90%); Espectro NMR (CDCl₃) 1.53 -1.77 (m, 6H), 1.79 -1.93 (m, 2H), 3.15 - 3.27 (m, 2H), 3.60 - 3.84 (m, 2H), 7.48 (d, 1H), 8.18 (dd, 1H), 8.30 (d, 1H); Espectro de masa MH⁺ 283.

Ejemplo de Referencia 38

5-Nitroindol-3-carbonitrilo

5-Nitroindol (2 g) se disolvió en éter dietílico (100 ml) y se enfrió a -10°C. Se agregó gota a gota isocianato de clorosulfonilo (5.37 ml) manteniendo una temperatura interna de -10°C para proporcionar un precipitado blanco. Éste se filtró y se lavó con éter antes de agregarlo a DMF (100 ml). La solución resultante se agitó a temperatura ambiente

durante 1 hora, luego se vertió en agua (500 ml) para proporcionar un sólido amarillo, el cual se filtró y se secó. Este sólido se agitó en acetato de etilo (250 ml) durante 30 minutos, luego se filtró. El filtrado se evaporó *in vacuo* para proporcionar el compuesto del título como un sólido amarillo pálido (1.35 g, 60%); Espectro NMR (DMSO-d₆) 7.7 (d, 1H), 8.2 (dd, 1H), 8.5 (m, 2H); Espectro de masa M-H⁺ 186.

Ejemplo de Referencia 39

Etil 4-(1-(*tert*-butoxicarbonil)piperidina)carboxilato

Manteniendo simultáneamente la temperatura en el rango 0-5 °C, se agregó en porciones una solución de dicarbonato di-*tert*-butílico (41.7 g) en acetato de etilo (75 ml) a una solución de 4-piperidinacarboxilato de etilo (30 g) en acetato de etilo (150 ml) enfriado a 5°C. Después de agitar durante 48 horas a temperatura ambiente, la mezcla se vertió en agua (300 ml). La capa orgánica se separó, se lavó sucesivamente con agua (200 ml), 0.1N ácido clorhídrico acuoso (200 ml), carbonato hidrogenado de sodio acuoso saturado (200 ml) y salmuera (200 ml), se secó y se evaporó para proporcionar el compuesto del título (48 g, 98%); Espectro NMR (CDCl₃) 1.25 (t, 3H), 1.45 (s, 9H), 1.55 -1.70 (m, 2H), 1.8 - 2.0 (d, 2H), 2.35 - 2.5 (m, 1H), 2.7 - 2.95 (t, 2H), 3.9 -4.1 (bs, 2H), 4.15 (q, 2H).

Ejemplo de Referencia 40

1-(*tert*-Butoxicarbonil)-4-hidroximetilpiperidina

Una solución de 1M hidruro de aluminio de litio en THF (133 ml) se agregó en porciones a una solución de 4-(1-(*tert*-butoxicarbonil)piperidina)carboxilato de etilo (Ejemplo de Referencia 39) (48 g) en THF seco (180 ml) enfriado a 0°C. Después de agitar a 0°C durante 2 horas, se agregó agua (30 ml) seguida por 2N hidróxido de sodio (10 ml). El precipitado se retiró por filtración a través de tierras de diatomeas y se lavó con acetato de etilo. El filtrado se lavó con agua, salmuera, se secó y se evaporó para proporcionar el compuesto del título (36.3 g, 89%); Espectro NMR (CDCl₃) 1.05 -1.2 (m, 2H), 1.35 -1.55 (m, 10H), 1.6-1.8 (m, 2H), 2.6 - 2.8 (t, 2H), 3.4-3.6 (t, 2H), 4.0 - 4.2 (bs, 2H); Espectro de masa M⁺ 215.

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567**Ejemplo de Referencia 41****1-(*tert*-Butoxicarbonil)-4-tosiloximetilpiperidina**

1,4-Diazabicyclo[2.2.2]octane (42.4 g) se agregó a una solución de 1-(*tert*-butoxicarbonil)-4-hidroximetilpiperidina (Ejemplo de Referencia 40) (52.5 g) en *tert*-butil metil éter (525 ml). Después de agitar durante 15 minutos a temperatura ambiente, la mezcla se enfrió a 5°C y una solución de cloruro de 4-toluenosulfonilo (62.8 g) en *tert*-butil metil éter (525 ml) se agregó en porciones durante 2 horas mientras se mantenía la temperatura a 0°C. Después de agitar durante 1 hora a temperatura ambiente, se agregó éter de petróleo (11). El precipitado se retiró por filtración. El filtrado se evaporó para proporcionar un sólido. El sólido se disolvió en éter y se lavó sucesivamente con 0.5N ácido clorhídrico acuoso (2 x 500 ml), agua, carbonato hidrogenado de sodio acuoso saturado y salmuera, se secó y se evaporó para proporcionar el compuesto del título como un sólido blanco (76.7 g, 85%); Espectro NMR (CDCl₃) 1.0-1.2 (m, 2H), 1.45 (s, 9H), 1.65 (d, 2H), 1.75 -1.9 (m, 2H), 2.45 (s, 3H), 2.55 - 2.75 (m, 2H), 3.85 (d, 1H), 4.0 - 4.2 (bs, 2H), 7.35 (d, 2H), 7.8 (d, 2H), Espectro de masa M+Na⁺ 392.

Ejemplo de Referencia 42**3-Etinil-4-(2-fluorobenciloxi)anilina**

Una solución de 4-(2-fluorobenciloxi)-3-(trimetilsililetinil)nitrobenceno (310 mg) (Ejemplo de Referencia 35) y 10% Pt/C en acetato de etilo / etanol (9:1, 10 ml) se agitó bajo una atmósfera de hidrógeno durante 20 minutos. El catalizador se retiró por filtración y la solución se concentró *in vacuo* para proporcionar un sólido verde. Éste se disolvió en metanol (100 ml) y DCM (50 ml), se agregó carbonato de potasio (0.375 g) y la solución se agitó durante 30 minutos. La reacción se filtró y se concentró *in vacuo*. El residuo se purificó por cromatografía usando DCM como eluyente para proporcionar el compuesto del título como un aceite amarillo (0.13 g, 62%); Espectro de masa MH⁺ 283.

El procedimiento descrito arriba se repitió usando el nitrobenceno apropiado. Así se obtuvo el compuesto descrito a continuación:

176
568**Ejemplo de Referencia 42.1****3-Etinil-4-(3-fluorobenciloxi)anilina**

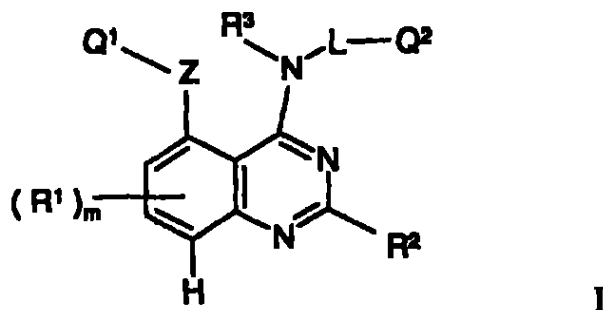
Obtenida de 4-(3-fluorobenciloxi)-3-(trimetilsililetinil)nitrobenceno (Ejemplo de Referencia 35.1); Espectro de masa MH^+ 283.

Ejemplo de Referencia 43**3-Fluoro-4-(1-metil-1*H*-imidazolil-2-iltio)nitrobenceno**

A una solución agitada de 2-mercapto-1-metilimidazol (1.14 g), en DMF (20 ml), se agregó hidruro de sodio (0.44 g) en pequeñas porciones y la reacción se agitó a temperatura ambiente hasta que cesó la efervescencia. A esto se agregó una solución de 3,4-difluoronitrobenceno (1.59 g) en DMF (10 ml), y la solución se agitó a 80°C durante 4 horas. La reacción se vertió en agua (150 ml) y el material orgánico se extrajo en acetato de etilo (150 ml). La capa orgánica se lavó sucesivamente con agua (3 x 150 ml), salmuera (150 ml) y se secó. La evaporación del solvente produjo un aceite que se purificó por cromatografía usando acetato de etilo y luego 10% metanol / acetato de etilo como eluyente para proporcionar el compuesto del título como un sólido (1.8 g, 70%); Espectro NMR (DMSO- d_6) 2.5 (s, 3H), 6.7 - 6.9 (t, 1H), 7.2 (t, 1H), 7.6 (s, 1H), 7.95 - 8.05 (dd, 1H), 8.15 - 8.25 (dd, 1H); Espectro de masa MH^+ 254.

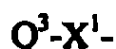
REIVINDICACIONES

1. Un derivado de quinazolina de la Fórmula I



en donde m es 0, 1 ó 2;

cada grupo R^1 , que puede ser el mismo o diferente, se selecciona de halógeno, trifluorometilo, ciano, isociano, nitro, hidroxilo, mercapto, amino, formilo, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N -(1-6C)alquilcarbamoilo, N,N -di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N -(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N -(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N -(1-6C)alquil-(3-6C)alquinoilamino, N -(1-6C)alquilsulfamoilo, N,N -di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N -(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^1 es un enlace directo o se selecciona de O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ y N(R⁴)C(R⁴)₂, en donde cada R⁴ es, independientemente, hidrógeno o (1-6C)alquilo, y Q³ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo, o (R¹)_m es (1-3C)alquilenodioxo,

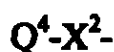
y en donde átomos de carbono adyacentes en cualquier cadena (2-

570



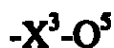
6C)alquileo en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH y C≡C en donde R⁵ es hidrógeno o (1-6C)alquilo,

y en donde cualquier GRUPO CH₂=CH- ó HC≡C- en un sustituyente R¹ lleva opcionalmente en la posición terminal CH₂= ó HC≡ un sustituyente seleccionado de halógeno, carboxi, carbamoilo, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquil o de un grupo de la fórmula:



en donde X² es un enlace directo o se selecciona de CO y N(R⁶)CO, en donde R⁶ es hidrógeno o (1-6C)alquilo, y Q⁴ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde cualquier grupo CH₂ ó CH₃ en un sustituyente R¹ lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxí, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X³ es un enlace directo o se selecciona de O, S, SO, SO₂, N(R⁷), CO, CH(OR⁷), CON(R⁷), N(R⁷)CO, SO₂N(R⁷), N(R⁷)SO₂, C(R⁷)₂O, C(R⁷)₂S y N(R⁷)C(R⁷)₂, en donde R⁷ es hidrógeno o (1-6C)alquilo, y Q⁵ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-



6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en R¹ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, amino(2-6C)alcanoilo, N-(1-6C)alquilamino(2-6C)alcanoilo, N,N-di-[(1-6C)alquil]amino(2-6C)alcanoilo, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X⁴ es un enlace directo o se selecciona de O y N(R⁹), en donde R⁹ es hidrógeno o (1-6C)alquilo, y R⁸ es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, carboxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo, (1-6C)alcoxicarbonilamino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxicarbonil-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X⁵ es un enlace directo o se selecciona de O, CO y N(R¹⁰), en donde R¹⁰ es hidrógeno o (1-6C)alquilo, y Q⁶ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los

mismos o diferentes, seleccionados de halógeno, hidroxilo, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

y en donde cualquier grupo heterociclilo en un sustituyente en R¹ lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

R² es hidrógeno;

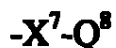
R³ es hidrógeno o (1-6C)alquilo;

Z es un enlace directo o se selecciona de O, S, SO, SO₂, N(R¹¹), CO, CH(OR¹¹), CON(R¹¹), N(R¹¹)CO, SO₂N(R¹¹), N(R¹¹)SO₂, OC(R¹¹)₂, SC(R¹¹)₂ y N(R¹¹)C(R¹¹)₂, en donde cada R¹¹ es, independientemente, hidrógeno o (1-6C)alquilo;

Q¹ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en el grupo Q¹-Z- se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R¹²), CO, CH(OR¹²), CON(R¹²), N(R¹²)CO, SO₂N(R¹²), N(R¹²)SO₂, CH=CH y C≡C en donde R¹² es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo CH₂ ó CH₃ en el grupo Q¹-Z- lleva opcionalmente en cada dicho grupo CH₂ ó CH₃ uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbanioilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X⁷ es un enlace directo o se selecciona de O, S, SO, SO₂, N(R¹⁴),

CO, CH(OR¹⁴), CON(R¹⁴), N(R¹⁴)CO, SO₂N(R¹⁴), N(R¹⁴)SO₂, C(R¹⁴)₂O, C(R¹⁴)₂S y N(R¹⁴)C(R¹⁴)₂, en donde R¹⁴ es hidrógeno o (1-6C)alquilo, y Q⁸ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, amino(2-6C)alcanoilo, N-(1-6C)alquilamino(2-6C)alcanoilo, N,N-di-[(1-6C)alquil]amino(2-6C)alcanoilo, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X⁸ es un enlace directo o se selecciona de O y N(R¹⁶), en donde R¹⁶ es hidrógeno o (1-6C)alquilo, y R¹⁵ es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alkylamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo, o de un grupo de la fórmula:

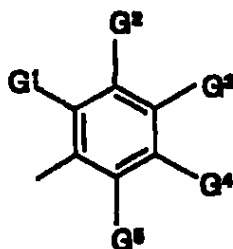


en donde X⁹ es un enlace directo o se selecciona de O, CO y N(R¹⁷), en donde R¹⁷ es hidrógeno o (1-6C)alquilo, y Q⁹ es arilo, aril-(1-6C)alquilo,

heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

Q² es un grupo arilo de fórmula Ia



Ia

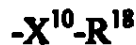
en donde G¹ y G⁵ son hidrógeno,

G² y G⁴ cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino, arilo y heteroarilo,

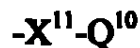
y en donde un grupo arilo o heteroarilo en cualquiera de G² y G⁴ lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

G³ se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N-N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-

6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

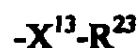


en donde X^{10} es un enlace directo o se selecciona de O y N(R^{19}), en donde R^{19} es hidrógeno o (1-6C)alquilo, y R^{18} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO, SO₂, N(R^{20}), CO, CH(OR²⁰), CON(R^{20}), N(R^{20})CO, SO₂N(R^{20}), N(R^{20})SO₂, C(R^{20})₂O, C(R^{20})₂S, C(R^{20})₂N(R^{20}) y N(R^{20})C(R^{20})₂, en donde R^{20} es hidrógeno o (1-6C)alquilo, y Q^{10} es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde Q^{10} lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, formilo, carbamoilo, sulfamoilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



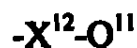
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en donde X^{13} es un enlace directo o se selecciona de O y N(R^{24}), en donde R^{24} es hidrógeno o (1-6C)alquilo, y R^{23} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxicarbonil-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,

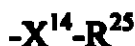
or G^3 y G^4 juntos forman un grupo de fórmula :- $-CH=CH-CH=CH-$, $-N=CH-CH=CH-$, $-CH=N-CH=CH-$, $-CH=CH-N=CH-$, $-CH=CH-CH=N-$, $-N=CH-N=CH-$, $-CH=N-CH=N-$, $-N=CH-CH=N-$, $-N=N-CH=CH-$, $-CH=CH-N=N-$, $-CH=CH-O-$, $-O-CH=CH-$, $-CH=CH-S-$, $-S-CH=CH-$, $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-$, $-CH_2-CH_2-S-$, $-S-CH_2-CH_2-$, $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, $-S-CH_2-S-$, $-S-CH_2-CH_2-S-$, $-CH=CH-NH-$, $-NH-CH=CH-$, $-CH_2-CH_2-NH-$, $-NH-CH_2-CH_2-$, $-N=CH-NH-$, $-NH-CH=N-$, $-NH-CH_2-NH-$, $-O-CH=N-$, $-N=CH-O-$, $-S-CH=N-$, $-N=CH-S-$, $-O-CH_2-NH-$, $-NH-CH_2-O-$, $-S-CH_2-NH-$, $-NH-CH_2-S-$, $-O-N=CH-$, $-CH=N-O-$, $-S-N=CH-$, $-CH=N-S-$, $-O-NH-CH_2-$, $-CH_2-NH-O-$, $-S-NH-CH_2-$, $-CH_2-NH-S-$, $-NH-N=CH-$, $-CH=N-NH-$, $-NH-NH-CH_2-$, $-CH_2-NH-NH-$, $-N=N-NH-$ o $-NH-N=N-$,

y el anillo heteroarilo o heterocíclico, bicíclico, de 9 o 10 miembros, formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la porción heteroarilo o heterocíclica del anillo bicíclico 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxi, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino y un grupo de la fórmula:



en donde X^{12} es un enlace directo o se selecciona de O, SO, SO₂, N(R^{21}), SO₂N(R^{21}) y CO, en donde R^{21} es hidrógeno o (1-6C)alquil y Q^{11} es arilo,

aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, formilo, carbamoilo, sulfamoilo, mercapto, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^{14} es un enlace directo o se selecciona de O y N(R^{26}), en donde R^{26} es hidrógeno o (1-6C)alquilo, y R^{25} es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo; y

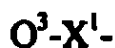
L es un enlace directo o $-[C(R^{22})_2]_n$, en donde n es 1 ó 2, y cada R^{22} independientemente es hidrógeno o (1-4C)alquilo,

y cuando L es un enlace directo, por lo menos uno de G^2 , G^3 y G^4 es distinto de H; o una sal farmacéuticamente aceptable del mismo.

2. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde m es como se define en la reivindicación 1 y

cada grupo R^1 , que puede ser el mismo o diferente, se selecciona de halógeno, trifluorometilo, ciano, isociano, nitro, hidroxilo, mercapto, amino,

formilo, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

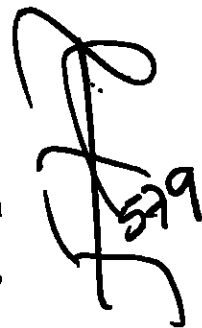


en donde X^1 es un enlace directo o se selecciona de O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ y N(R⁴)C(R⁴)₂, en donde cada R⁴ es, independientemente, hidrógeno o (1-6C)alquilo, y Q³ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenal-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterocicilil-(1-6C)alquilo, o (R¹)_m es (1-3C)alquilenodioxo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH y C≡C en donde R⁵ es hidrógeno o (1-6C)alquilo,

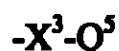
y en donde cualquier grupo CH₂=CH- ó HC≡C- en un sustituyente R¹ lleva opcionalmente en la posición terminal CH₂= ó HC≡ un sustituyente seleccionado de halógeno, carboxi, carbamoilo, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquil o de un grupo de la fórmula:





en donde X^2 es un enlace directo o se selecciona de CO y $N(R^6)CO$, en donde R^6 es hidrógeno o (1-6C)alquilo, y Q^4 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo CH_2 ó CH_3 en un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



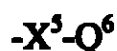
en donde X^3 es un enlace directo o se selecciona de O, S, SO, SO_2 , $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ y $N(R^7)C(R^7)_2$, en donde R^7 es hidrógeno o (1-6C)alquilo, y Q^5 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino,

N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^4 es un enlace directo o se selecciona de O y N(R^9), en donde R^9 es hidrógeno o (1-6C)alquilo, y R^8 es halógeno-(1-6C)alquilo, hidroxí-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo o (1-6C)alcoxycarbonilamino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^5 es un enlace directo o se selecciona de O, CO y N(R^{10}), en donde R^{10} es hidrógeno o (1-6C)alquilo, y Q^6 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

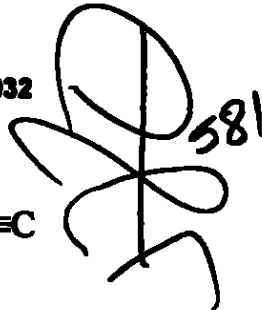
R^2 es hidrógeno;

R^3 es hidrógeno o (1-6C)alquilo;

Z es un enlace directo o se selecciona de O, S, SO, SO₂ N(R^{11}), CO, CH(OR¹¹), CON(R^{11}), N(R^{11})CO, SO₂N(R^{11}), N(R^{11})SO₂, OC(R^{11})₂, SC(R^{11})₂ y N(R^{11})C(R^{11})₂, en donde cada R^{11} es, independientemente, hidrógeno o (1-6C)alquilo;

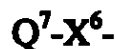
Q^1 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en el grupo Q^1 -Z- se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO₂, N(R^{12}), CO,



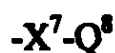
$\text{CH}(\text{OR}^{12})$, $\text{CON}(\text{R}^{12})$, $\text{N}(\text{R}^{12})\text{CO}$, $\text{SO}_2\text{N}(\text{CR}^{12})$, $\text{N}(\text{R}^{12})\text{SO}_2$, $\text{CH}=\text{CH}$ y $\text{C}\equiv\text{C}$ en donde R^{12} es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo $\text{CH}_2=\text{CH}-$ ó $\text{HC}\equiv\text{C}-$ en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente en la posición terminal $\text{CH}_2=$ ó $\text{HC}\equiv$ un sustituyente seleccionado de halógeno, carboxi, carbamoilo, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquilo o de un grupo de la fórmula:

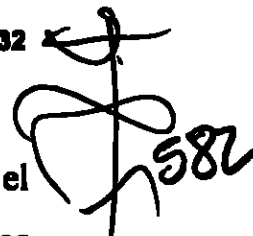


en donde X^6 es un enlace directo o se selecciona de CO y $\text{N}(\text{R}^{13})\text{CO}$, en donde R^{13} es hidrógeno o (1-6C)alquilo, y Q^7 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo CH_2 ó CH_3 en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



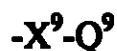
en donde X^7 es un enlace directo o se selecciona de O , S , SO , SO_2 , $\text{N}(\text{R}^{14})$, CO , $\text{CH}(\text{OR}^{14})$, $\text{CON}(\text{R}^{14})$, $\text{N}(\text{R}^{14})\text{CO}$, $\text{SO}_2\text{N}(\text{R}^{14})$, $\text{N}(\text{R}^{14})\text{SO}_2$, $\text{C}(\text{R}^{14})_2\text{O}$, $\text{C}(\text{R}^{14})_2\text{S}$ y $\text{N}(\text{R}^{14})\text{C}(\text{R}^{14})_2$, en donde R^{14} es hidrógeno o (1-6C)alquilo, y Q^8 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,



y en donde cualquier grupo arilo, heteroarilo o heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



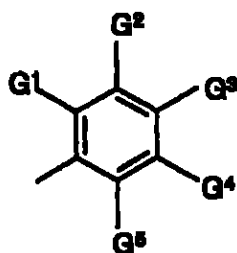
en donde X⁸ es un enlace directo o se selecciona de O y N(R¹⁶), en donde R¹⁶ es hidrógeno o (1-6C)alquilo, y R¹⁵ es halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X⁹ es un enlace directo o se selecciona de O, CO y N(R¹⁷), en donde R¹⁷ es hidrógeno o (1-6C)alquilo, y Q⁹ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

Q² es un grupo arilo de fórmula Ia



Ia

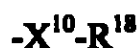
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en donde G^1 y G^5 son hidrógeno,

G^2 y G^4 cada uno independientemente se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino, arilo y heteroarilo,

y en donde un grupo arilo o heteroarilo en cualquiera de G^2 y G^4 lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino y di-[(1-6C)alquil]amino,

G^3 se selecciona de hidrógeno, halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^{10} es un enlace directo o se selecciona de O y $N(R^{19})$, en donde

R^{19} es hidrógeno o (1-6C)alquilo, y R^{18} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, SO, SO₂, N(R²⁰), CO, CH(OR²⁰), CON(R²⁰), N(R²⁰)CO, SO₂N(R²⁰), N(R²⁰)SO₂, C(R²⁰)₂O, C(R²⁰)₂S y N(R²⁰)C(R²⁰)₂, en donde R²⁰ es hidrógeno o (1-6C)alquilo, y Q¹⁰ es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

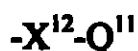
y en donde Q¹⁰ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino,

y en donde cualquier grupo heterociclilo en Q¹⁰ lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo,

o G³ y G⁴ juntos forman un grupo de fórmula:- CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, -CH=CH-CH=N-, -N=CH-N=CH-, -CH=N-CH=N-, -N=CH-CH=N-, -N=N-CH=CH-, -CH=CH-N=N-, -CH=CH-O-, -O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH₂-CH₂-O-, -O-CH₂-CH₂-, -CH₂-CH₂-S-, -S-CH₂-CH₂-, -O-CH₂-O-, -O-CH₂-CH₂-O-, -S-CH₂-S-, -S-CH₂-CH₂-S-, -CH=CH-NH-, -NH-CH=CH-, -CH₂-CH₂-NH-, -NH-CH₂-CH₂-, -N=CH-NH-, -NH-CH=N-, -NH-CH₂-NH-

, -O-CH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH₂-NH-, -NH-CH₂-O-, -S-CH₂-NH-, -NH-CH₂-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -CH=N-S-, -O-NH-CH₂-, -CH₂-NH-O-, -S-NH-CH₂-, -CH₂-NH-S-, -NH-N=CH-, -CH=N-NH-, -NH-NH-CH₂-, -CH₂-NH-NH-, -N=N-NH- o -NH-N=N-,

y el anillo heteroarilo o heterocíclico, bicíclico, de 9 o 10 miembros, formado cuando G³ y G⁴ juntos se enlazan lleva opcionalmente en la porción heteroarilo o heterocíclica del anillo bicíclico 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, o de un grupo de la fórmula:



en donde X¹² es un enlace directo o se selecciona de O, SO, SO₂, N(R²¹) y CO, en donde R²¹ es hidrógeno o (1-6C)alquilo y Q¹¹ es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi, y cualquier anillo heterocíclico bicíclico así formado lleva opcionalmente 1 ó 2 grupos oxo o tioxo; y

L es un enlace directo o -[C(R²²)₂]_n, en donde n es 1 ó 2, y cada R²² independientemente es hidrógeno o (1-4C)alquilo,

y cuando L es un enlace directo, por lo menos uno de G², G³ y G⁴ es distinto de H; o una sal farmacéuticamente aceptable del mismo.

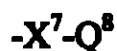
3. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de m, R¹, R², R³, L y Q² es como se define en la reivindicación 1 y

Z se selecciona de O, S, SO, SO₂, N(R¹¹), CO, CH(OR¹¹), CON(R¹¹), N(R¹¹)CO, SO₂N(R¹¹), N(R¹¹)SO₂, OC(R¹¹)₂, SC(R¹¹)₂ y N(R¹¹)C(R¹¹)₂, en donde R¹¹ es hidrógeno o (1-6C)alquilo; y

Q¹ se selecciona de (3-7C)cicloalquilo, (3-7C)cicloalquenilo y

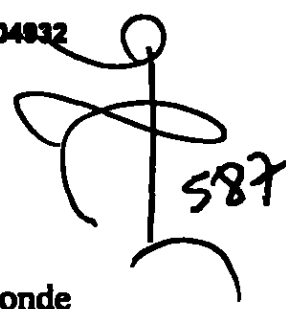
heterociclilo,

y en donde cualquier grupo CH_2 ó CH_3 en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o sustituyentes (1-6C)alquilo o un sustituyente seleccionado de hidroxilo, ciano, amino, carboxi, carbamoilo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:



en donde X^7 es un enlace directo o se selecciona de O, S, SO, SO_2 , $\text{N}(\text{R}^{14})$, CO, $\text{CH}(\text{OR}^{14})$, $\text{CON}(\text{R}^{14})$, $\text{N}(\text{R}^{14})\text{CO}$, $\text{SO}_2\text{N}(\text{R}^{14})$, $\text{N}(\text{R}^{14})\text{SO}_2$, $\text{C}(\text{R}^{14})_2\text{O}$, $\text{C}(\text{R}^{14})_2\text{S}$ y $\text{N}(\text{R}^{14})\text{C}(\text{R}^{14})_2$, en donde R^{14} es hidrógeno o (1-6C)alquilo, y Q^8 es (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heterociclilo o heterocicli-(1-6C)alquilo,

y en donde cualquier grupo heterociclilo en el grupo $\text{Q}^1\text{-Z-}$ lleva opcionalmente 1, 2 ó 3 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxilo, amino, carboxi, carbamoilo, formilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxycarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, amino(2-6C)alcanoilo, N-(1-6C)alquilamino(2-6C)alcanoilo, N,N-di-[(1-6C)alquil]amino(2-6C)alcanoilo, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de



un grupo de la fórmula:



en donde X^8 es un enlace directo o se selecciona de O y N(R^{16}), en donde R^{16} es hidrógeno o (1-6C)alquilo, y R^{15} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, carboxi-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, carbamoil-(1-6C)alquilo, N-(1-6C)alquilcarbamoil-(1-6C)alquilo, N,N-di-[(1-6C)alquil]carbamoil-(1-6C)alquilo, (2-6C)alcanoil-(1-6C)alquilo o (1-6C)alcoxycarbonil-(1-6C)alquilo, o de un grupo de la fórmula:



en donde X^9 es un enlace directo o se selecciona de O, CO y N(R^{17}), en donde R^{17} es hidrógeno o (1-6C)alquilo, y Q^9 es heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, (1-6C)alquilo y (1-6C)alcoxi, y en donde cualquier grupo heterociclilo en el grupo Q^1 -Z- lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo.

4. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R^2 , R^3 , 1, Z, Q^1 y Q^2 es como se define en la reivindicación 1 y

m es 1; y

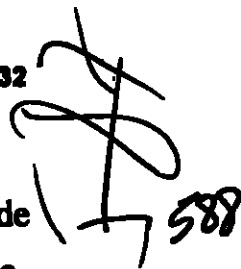
el grupo R^1 se localiza en la posición 7 y es un grupo de la fórmula :



en donde X^1 es O y Q^3 se selecciona de heterociclil-propilo o heterociclil-butilo, en donde dicho grupo heterociclilo contiene por lo menos 1 átomo de nitrógeno,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquilenos en un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, N(R^5), CO, CH=CH y C≡C en donde R^5 es hidrógeno o (1-6C)alquilo,

y en donde cualquier grupo heterociclilo en R^1 lleva opcionalmente 1



ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, carbamoilo, (1-4C)alquilo, (1-4C)alcoxi, (2-4C)alquenilo, (2-4C)alquinilo, (2-4C)alcanoilo, (1-4C)alquilsulfonilo, (1-4C)alcoxycarbonilo, N-(1-4C)alquilcarbamoilo y N,N-di-[(1-4C)alquil]carbamoilo, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:



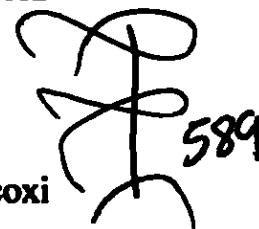
en donde X^4 es un enlace directo o se selecciona de O y NH, y R^8 es 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, fluorometilo, 2-fluoroetilo, clorometilo, 2-cloroetilo, acetilmetilo, acetamidometilo, carbamoilmetilo, 2-carbamoiletilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-dimetilcarbamoil)etilo, cianometilo, cianoetilo, metoxycarbonilaminometilo o etoxycarbonilaminometilo, y en donde cualquier grupo heterocíclico en R^1 lleva opcionalmente 1 sustituyente oxo.

5. Un derivado de quinazolina de acuerdo con la reivindicación 1 o la reivindicación 2, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R^2 , R^3 , 1, Z, Q^1 y Q^2 es como se define en la reivindicación 1 o la reivindicación 2, y

m es 1; y

el grupo R^1 se localiza en la posición 7 y se selecciona de hidroxilo, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R^1 se separan opcionalmente por la inserción



en la cadena de un grupo seleccionado de O, NH y N(CH₃),

y en donde cualquier grupo terminal CH₃ en una cadena (1-6C)alcoxi en un sustituyente R¹ lleva opcionalmente en el grupo terminal CH₃ un sustituyente seleccionado de hidroxilo, amino y N-(1-metilpirrolidin-3-il)-N-metilamino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R¹ lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en un sustituyente R¹ lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahidrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo.

6. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R², R³, L, Z, Q¹ y Q² es como se define en la reivindicación 1 y

m es 1; y

el grupo R¹ se localiza en la posición 7 y es (1-3C)alcoxi o (1-3C)alcoxi(1-3C)alcoxi.

7. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R¹, R², R³, m, L y Q² es como se define en la reivindicación 1 y

Z es O; y

El grupo Q¹-Z- se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo, y

en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q¹ lleva opcionalmente un sustituyente seleccionado de metilo, etilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, 2-fluoroetilo, 2-metoxietil carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, acetilmetilo y metoxycarbonilmetilo, y

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en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q¹-Z- lleva opcionalmente 1 sustituyente oxo.

8. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R¹, R², R³, m, L y Q² es como se define en la reivindicación 1 y

Z es O; y

Q¹ se selecciona de tetrahydrofuran-3-ilo, tetrahidropiran-3-ilo y tetrahidropiran-4-ilo,

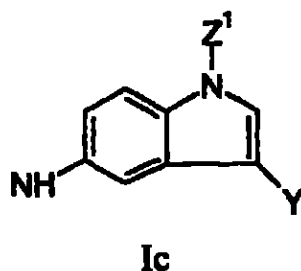
y en donde cualquier grupo tetrahydrofuranilo o tetrahidropiranilo en Q¹ lleva opcionalmente 1 ó 2 sustituyentes seleccionados de fluoro, cloro, hidroxilo, metilo, etilo y amino, y

en donde cualquier grupo tetrahydrofuranilo o tetrahidropiranilo en el grupo Q¹-Z- lleva opcionalmente 1 sustituyente oxo.

9. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R¹, R², m, Z y Q¹ es como se define en la reivindicación 1 y

el grupo Q²LN(R³) se selecciona de 3-cloro-4-fluoroanilino, 3-cloro-4-hidroxianilino, 3-fluoroanilino, 3-bromoanilino, 3-cloroanilino, 3-metilanilino y 3-etilanilino.

10. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R¹, R², m, Z y Q¹ es como se define en la reivindicación 1 y el grupo Q²LN(R³) es un grupo de la fórmula Ic:

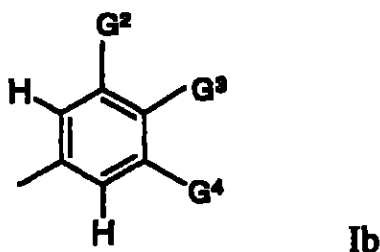


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en donde Z^1 es hidrógeno o (1-4C)alquilo, y Y se selecciona de hidrógeno, halógeno, (1-4C)alquilo y ciano.

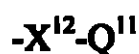
11. Un derivado de quinazolina de acuerdo con la reivindicación 1 o la reivindicación 2, o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R^1 , R^2 , R^3 , m, L, Z y Q^1 es como se define en la reivindicación 1 o la reivindicación 2, y

Q^2 es un grupo arilo de fórmula Ib:



en donde G^3 y G^4 juntos forman un grupo de fórmula:- $-NH-CH=CH-$ o $-NH-N=CH-$,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 se enlazan juntos lleva opcionalmente en un grupo NH de la porción heteroarilo del anillo bicíclico un grupo de la fórmula:



en donde X^{12} es un enlace directo o es SO_2 y Q^{11} es bencilo o 2-piridilmetilo, el cual lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, hidroxilo y metilo,

y el anillo heteroarilo bicíclico de 9 miembros formado cuando G^3 y G^4 juntos se enlazan lleva opcionalmente en la posición 3 en la porción heteroarilo del anillo bicíclico 1 sustituyente seleccionado de fluoro, cloro, bromo, ciano, hidroxilo, amino, metilo, etilo y etinilo,

y G^2 se selecciona de hidrógeno, fluoro, cloro, bromo, ciano, hidroxilo, amino, metilo, etilo y etinilo.

12. Un derivado de quinazolina de acuerdo con la reivindicación 1, o una

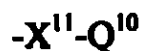
sal farmacéuticamente aceptable del mismo, en donde cada uno de R^2 , R^3 , Z , L y Q^1 son como se define en la reivindicación 1 y

Q^2 es un grupo de fórmula Ia como se define en la reivindicación 1 en donde:

G^1 , G^2 y G^3 son hidrógeno,

G^4 se selecciona de hidrógeno, halógeno, (1-6C)alquilo y (2-6C)alquinilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} se selecciona de bencilo y heteroaril-metilo, y en donde cualquier grupo fenilo o heteroarilo en Q^{10} lleva opcionalmente 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de halógeno, hidroxilo, ciano, amino, (1-6C)alquilo, (1-6C)alcoxi, (1-6C)alquilamino y di-[(1-6C)alquil]amino, carbamoilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, halógeno-(1-6C)alquilo, hidroxilo-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alil]amino-(1-6C)alquilo, carbamoilo-(1-6C)alquilo, N-(1-6C)alquilcarbamoilo-(1-6C)alquilo y N,N-di-[(1-6C)alquil]carbamoilo-(1-6C)alquilo;

m es 1; y

R^1 se localiza en la posición 7 y es como se define en la reivindicación 1.

13. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente, se localiza en la posición 7 y se selecciona de hidroxilo, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-morfolinoetoxi,

3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH y N(CH₃),

y en donde cualquier grupo terminal CH₃ en una cadena (1-6C)alcoxi en un sustituyente R¹ lleva opcionalmente en dicho grupo terminal CH₃ un sustituyente seleccionado de hidroxilo, amino y N-(1-metilpirrolidin-3-il)-N-metilamino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R¹ lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en un sustituyente R¹ lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahydrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo;

el grupo Q¹-Z- se selecciona de ciclopentiloxi, tetrahydrofuran-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, 1-oxotetrahidrotiopiran-4-iloxi, tetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, 1-oxotetrahidrotien-3-iloxi, pirrolidin-3-iloxi, pirrolidin-2-iloxi, piperidin-3-iloxi, piperidin-4-iloxi, homopiperidin-3-iloxi, homopiperidin-4-iloxi y azetidin-3-iloxi,

y en donde el grupo azetidinilo, pirrolidinilo, piperidinilo u homopiperidinilo en el grupo Q¹-Z- es opcionalmente N- sustituido por un sustituyente seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, tert-butilo, alilo, 2-propinilo, acetilo, propionilo, metoxycarbonilo, etoxycarbonilo, propoxycarbonilo, tert-butoxycarbonilo, metilsulfonilo, etilsulfonilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-dimetilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-dimetilcarbamoil)etilo, acetilmetilo, 2-acetiletilo, metoxycarbonilmetilo y 2-metoxycarboniletilo,

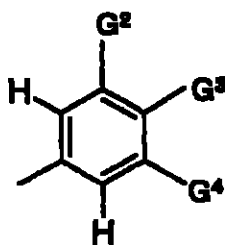
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y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

R² y R³ son hidrógeno;

L es un enlace directo; y

Q² es un grupo arilo de fórmula Ib



Ib

en donde G² es hidrógeno, y G³ y G⁴, que puede ser el mismo o diferente, se selecciona de hidrógeno, fluoro, cloro, bromo, ciano, hidroxilo, metilo, etilo, y etinilo, a condición que por lo menos uno de G³ y G⁴ es distinto de hidrógeno, o G³ y G⁴ juntos forman un grupo de fórmula:- -CH=CH-NH-, -NH-CH=CH-, -NH-N=CH-, -CH=N-NH-, y el anillo heteroarilo bicíclico de 9 miembros así formado lleva opcionalmente en la porción heteroarilo del anillo bicíclico 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, y metilo; o una sal de adición de ácido farmacéuticamente aceptable del mismo.

14. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 en donde: m es 1 y el grupo R¹ se localiza en la posición 7 y se selecciona de hidroxilo, amino, metilo, etilo, propilo, metoxi, etoxi, propoxi, butoxi, pentoxi, pirrolidin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-homopiperidinoetoxi, 3-homopiperidinopropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alcoxi en un sustituyente R¹ se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH y N(CH₃),

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y en donde cualquier grupo terminal CH₃ en una cadena (1-6C)alcoxi en un sustituyente R¹ lleva opcionalmente en el grupo terminal CH₃ un sustituyente seleccionado de hidroxilo, amino y N-(1-metilpirrolidin-3-il)-N-metilamino,

y en donde cualquier grupo pirrolidinilo o piperidinilo en un sustituyente R¹ lleva opcionalmente un sustituyente seleccionado de hidroxilo, metilo, amino, metilamino y dimetilamino,

y en donde cualquier grupo piperazin-1-ilo u homopiperazin-1-ilo en un sustituyente R¹ lleva opcionalmente un sustituyente en la posición 4 seleccionado de metilo, etilo, isopropilo, 2-metoxietilo, tetrahydrofurfurilo, 2-morfolinoetilo y 1-metilpiperidin-4-ilo;

el grupo Q¹-Z- se selecciona de ciclopentilo, tetrahydrofuran-3-ilo, tetrahidropiran-4-ilo, tetrahidrotiopiran-4-ilo, 1,1-dioxotetrahidrotiopiran-4-ilo, 1-oxotetrahidrotiopiran-4-ilo, tetrahidrotien-3-ilo, 1,1-dioxotetrahidrotien-3-ilo, 1-oxotetrahidrotien-3-ilo, pirrolidin-3-ilo, pirrolidin-2-ilo, piperidin-3-ilo, piperidin-4-ilo, homopiperidin-3-ilo, homopiperidin-4-ilo y azetidín-3-ilo,

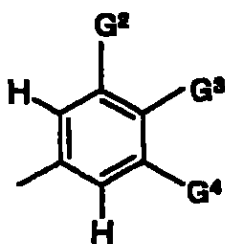
y en donde el grupo azetidínilo, pirrolidinilo, piperidinilo u homopiperidinilo en el grupo Q¹-Z- es opcionalmente N- sustituido por un sustituyente seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, tert-butilo, alilo, 2-propinilo, acetilo, propionilo, metoxicarbonilo, etoxicarbonilo, propoxicarbonilo, tert-butoxicarbonilo, metilsulfonilo, etilsulfonilo, 2-metoxietilo, carbamoilmetilo, N-metilcarbamoilmetilo, N,N-di-metilcarbamoilmetilo, 2-carbamoiletilo, 2-(N-metilcarbamoil)etilo, 2-(N,N-di-metilcarbamoil)etilo, acetilmetilo, 2-acetiletilo, metoxicarbonilmetilo y 2-metoxicarboniletilo,

y en donde cualquier grupo heterociclilo en el grupo Q¹-Z- lleva opcionalmente 1 ó 2 sustituyentes oxo;

R² y R³ son hidrógeno;

L es un enlace directo; y

Q² es un grupo arilo de fórmula Ib



Ib

en donde G^3 es un grupo de la fórmula:



en donde X^{11} es un enlace directo o se selecciona de O, S, $N(R^{20})$, CO, $CH(OR^{20})$ y $C(R^{20})_2NR^{20}$, en donde R^{20} es hidrógeno o metilo, y Q^{10} es un grupo fenilo o bencilo el cual se sustituye opcionalmente con 1 ó 2 sustituyentes seleccionados de fluoro, cloro, bromo, trifluorometilo, nitro, metilo, etilo, isopropilo, etinilo y ciano, o Q^{10} es una fracción heteroarilo seleccionada de 2-1H-imidazolilo, 2-1H-imidazolilmetilo, 4-tiazolilmetilo, 2-tienilmetilo, 1,2,5-tiadiazol-3-ilo, 1,2,5-tiadiazol-3-ilmetilo, 3-isoxazolilmetilo, 2-, 3- ó 4-piridilo, 2-, 3- ó 4-piridilmetilo, 8-quinolinilo, y 8-quinolinilmetilo, la cual fracción heteroarilo se sustituye opcionalmente con uno o dos sustituyentes seleccionados de fluoro, cloro, bromo, trifluorometilo, metilo, etinilo y ciano, y cada uno de G^2 y G^4 independientemente se seleccionan de hidrógeno, fluoro, cloro, bromo, metilo, y etinilo; o una sal farmacéuticamente aceptable del mismo.

15. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de 3-pirrolidin-1-ilpropoxi, 3-pirrolidin-2-ilpropoxi, 3-pirrolidin-3-ilpropoxi, 3-morfolinopropoxi, 3-piperidinopropoxi, 3-piperidin-2-ilpropoxi, 3-piperidin-3-ilpropoxi, 3-piperidin-4-ilpropoxi y 3-piperazin-1-ilpropoxi,

y en donde cualquier grupo heterociclilo en un sustituyente R^1 lleva opcionalmente un sustituyente seleccionado de hidroxilo, carbamoilo, metilo, etilo, alilo, acetilo, N-metilcarbamoil N,N-dimetilcarbamoilo, 2-metoxietilo, carbamoilmetilo, N,N-dimetilcarbamoilmetilo, acetilmetilo y

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cianometilo, y en donde cualquier grupo heterociclilo en un sustituyente en R^1 lleva opcionalmente 1 sustituyente oxo;

Z es O;

Q^1 es tetrahydrofuran-3-ilo, tetrahydropiran-4-ilo o tetrahydropiran-3-ilo,

R^2 es hidrógeno; y

$Q^2LN(R^3)$ se selecciona de 3-cloro-4-fluoroanilino, 3-fluoroanilino, 3-bromoanilino, 3-cloroanilino, 3-metilanilino y 3-etilanilino; o una sal farmacéuticamente aceptable del mismo.

16. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 en donde:

m es 0 ó 1 y el grupo R^1 , cuando está presente se localiza en la posición 7 y se selecciona de (1-3C)alcoxi y (1-3C)alcoxi(1-3C)alcoxi;

Z es O;

Q^1 se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo, y en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q^1 lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, o de un grupo de la fórmula:

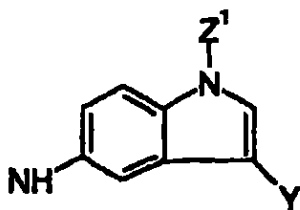


en donde X^8 es un enlace directo y R^{15} es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-dimetilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo, y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q^1 -Z- lleva opcionalmente 1 sustituyente oxo;

R^2 es hidrógeno; y

$Q^2LN(R^3)$ es un grupo de la fórmula Ic:

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Ic

en donde Z^1 es hidrógeno o (1-4C)alquilo, y

Y se selecciona de hidrógeno, halógeno, (1-4C)alquilo y ciano; o una sal farmacéuticamente aceptable del mismo.

17. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-3C)alcoxi y (1-3C)alcoxi(1-3C)alcoxi;

Z es O;

Q^1 se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo, y en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q^1 lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo y N,N-dimetilcarbamoilo, o de un grupo de la fórmula:



en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-dimetilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo, y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q^1 -Z- lleva opcionalmente 1 sustituyente oxo;

R^2 y R^3 son hidrógeno;

L es un enlace directo; y

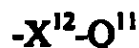
Q^2 es un grupo de fórmula la como se define en la reivindicación 1 en donde:

G^1 , G^2 y G^3 son hidrógeno, y

G^3 y G^4 juntos forman un grupo de la fórmula: $-NH-CH=CH-$, y el



anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye en la posición 1 por un grupo de la fórmula:



en donde X^{12} es un enlace directo y Q^{11} es bencilo el cual se sustituye opcionalmente por 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, bromo, ciano, metilo y etilo, y en donde el anillo indolilo así formado por G^3 y G^4 junto con los átomos de carbono a los cuales se unen se sustituye opcionalmente en la posición 3 por un sustituyente seleccionado de cloro y bromo; o una sal farmacéuticamente aceptable del mismo.

18. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-3C)alcoxi, (1-3C)alcoxi(1-3C)alcoxi y piperidin-4-ilmetoxi;

Z es O;

Q^1 se selecciona de pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo y tetrahidropiran-4-ilo, y en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q^1 lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, o de un grupo de la fórmula:



en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-di-metilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo, y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q^1-Z lleva opcionalmente 1 sustituyente oxo;

R^2 y R^3 son hidrógeno;

L es un enlace directo; y

Q^2 es un grupo de fórmula Ia como se define en la reivindicación 1 en

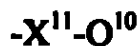
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donde:

G^1 , G^2 y G^5 son hidrógeno,

G^4 se selecciona de cloro, metilo y etinilo, y

G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} es bencilo el cual se sustituye opcionalmente por 1 ó 2 sustituyentes, que pueden ser los mismos o diferentes, seleccionados de fluoro, ciano y metilo; o una sal farmacéuticamente aceptable del mismo.

19. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 en donde:

m es 1 y el grupo R^1 se localiza en la posición 7 y se selecciona de (1-3C)alcoxi y (1-3C)alcoxi(1-3C)alcoxi;

Z es O;

Q^1 se selecciona de pirrolidin-3-ilo, piperidin-3-ilo y piperidin-4-ilo, y en donde cualquier grupo NH en un grupo pirrolidinilo o piperidinilo en Q^1 lleva opcionalmente un sustituyente seleccionado de (1-3C)alquilo, alilo, acetilo, carbamoilo, metoxycarbonilo, etoxycarbonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, o de un grupo de la fórmula:



en donde X^8 es un enlace directo, y R^{15} es halógeno-(1-3C)alquilo, metoxi-(1-3C)alquilo, etoxi-(1-3C)alquilo, carbamoil-(1-3C)alquilo, N-metilcarbamoil-(1-3C)alquilo, N,N-di-metilcarbamoil-(1-3C)alquilo, acetil-(1-3C)alquilo o metoxycarbonil-(1-3C)alquilo, y en donde cualquier grupo pirrolidinilo o piperidinilo en el grupo Q^1 -Z- lleva opcionalmente 1 sustituyente oxo;

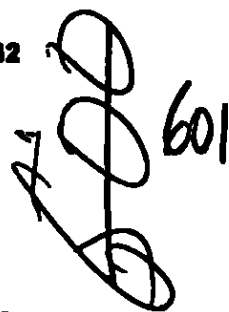
R^2 y R^3 son hidrógeno;

L es un enlace directo; y

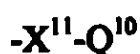
Q^2 es un grupo de fórmula Ia como se define en la reivindicación 1 en donde:

G^1 , G^2 y G^5 son hidrógeno,

G^4 se selecciona de cloro y metil , y



G^3 es un grupo de la fórmula:



en donde X^{11} es O y Q^{10} se selecciona de isoxazolilmetilo y tiazolilmetilo, y en donde el grupo heteroarilo en Q^{10} lleva opcionalmente un sustituyente metilo; o una sal farmacéuticamente aceptable del mismo.

20. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 seleccionado de: 4-(3-cloroanilino)-7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloroindol-5-ilamino)-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-bromoanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloroindol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-etinilanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloroanilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 7-metoxi-4-(3-metilanilino)-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-bromoanilino)-7-(2-metoxietoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-7-metoxi-5-(piperidin-4-iloxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(3-(piperidin-1-il)propoxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-5-(1-metilpiperidin-4-iloxi)-7-(2-(4-isopropil-piperazin-1-il)etoxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-7-[3-(*N*-(2-hidroxietil)-*N*-metilamino)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-7-[3-(*N*-(2-dimetilaminoetil)-*N*-metilamino)propoxi]-5-(tetrahidropiran-4-iloxi)quinazolina; y 4-(3-cloro-4-fluoroanilino)-7-(3-(4-metilpiperazin-1-il)propoxi)-5-(tetrahidrofuran-3-iloxi)quinazolina; o una sal de adición de ácido farmacéuticamente aceptable del mismo.

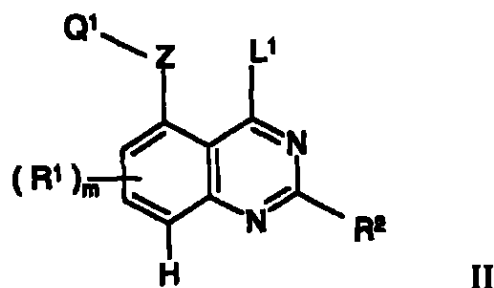
21. Un derivado de quinazolina de la Fórmula I como se define en la reivindicación 1 seleccionado de:
4-(3-bromoanilino)-7-(3-(*R*)-dimetilaminopirrolidin-1-il)-5-(1-

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metilpiperidin-4-iloxi)quinazolina; 4-(3-bromoindol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloro-4-benciloxianilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloro-4-(3-fluorobenciloxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-metil-4-(5-metilisoxazol-3-ilmetoxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-metil-4-(tiazol-4-ilmetoxi)anilino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(1-(3-fluorobencil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(1-(2-fluorobencil)indol-5-ilamino)-7-metoxi-5-(1-metilpiperidin-4-iloxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-7-(3-morfolinopropoxi)-5-(tetrahidrofuran-3-iloxi)quinazolina; 4-(3-cloro-4-fluoroanilino)-7-(3-pirrolidin-1-ilpropoxi)-5-(tetrahidrofuran-3-iloxi)quinazolina; 2-[4-(4-(3-cloro-4-fluoroanilino)-7-metoxiquinazolin-5-iloxi)piperidin-1-il]acetamida; 4-(3-cloro-4-fluoroanilino)-7-(2-metoxietoxi)-5-(1-metilpiperidin-4-iloxi)quinazolina; y 4-(3-cloro-4-fluoroanilino)-7-[3-(4-(N,N-dimetilcarbamoilmetil)piperazin-1-il)propoxi]-5-(tetrahidrofuran-3-iloxi)quinazolina; o una sal de adición de ácido farmacéuticamente aceptable del mismo.

22. Un proceso para la preparación de un derivado de quinazolina de la Fórmula I, o una sal del mismo, de acuerdo con la reivindicación 1 que comprende:

(a) la reacción de una quinazolina de la Fórmula II



en donde L¹ es un grupo desplazable y Q¹, Z, m, R¹ y R² son como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, con un compuesto de la Fórmula:

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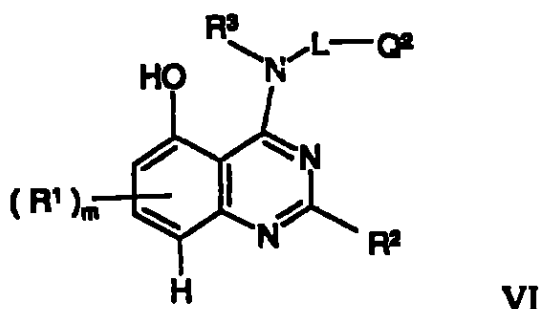
en donde Q^2 , L y R^3 son como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, a partir de lo cual cualquier grupo protector que esté presente se retira por medios tradicionales;

o

(b) para la producción de aquellos compuestos de la Fórmula I en donde Z es un átomo de oxígeno, el acoplamiento, convenientemente en la presencia de un agente deshidratante apropiado, de un alcohol de la Fórmula:



en donde Q^1 es como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, con una quinazolina de la Fórmula VI

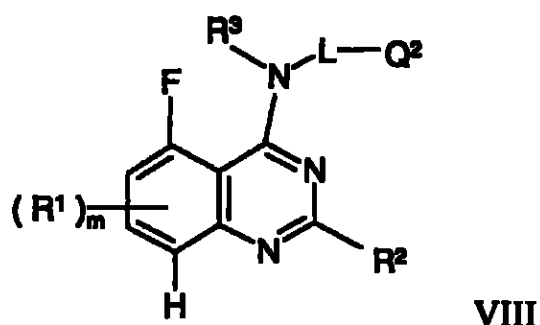


en donde m, R^1 , R^2 , R^3 , L y Q^2 son como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, a partir de lo cual cualquier grupo protector que esté presente se retira por medios tradicionales; o

(c) para la producción de aquellos compuestos de la Fórmula I en donde Z es O, la reacción de un alcohol de la Fórmula

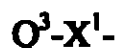


en donde Q^1 es como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, con una quinazolina de la Fórmula VIII

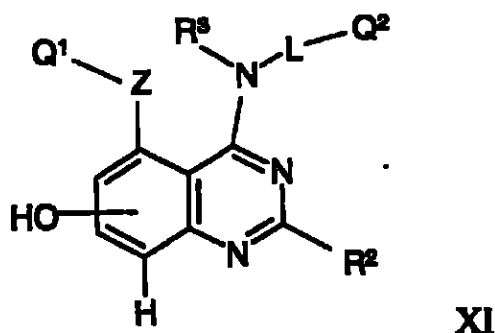


en donde m , R^1 , R^2 , R^3 , L y Q^2 son como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, a partir de lo cual cualquier grupo protector que esté presente se retira por medios tradicionales; o

(d) para la producción de aquellos compuestos de la Fórmula I en donde m es 1 y R^1 es un grupo de la fórmula



en donde Q^3 es un grupo aril-(1-6C)alquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroaril-(1-6C)alquilo o heterociclí-(1-6C)alquilo y X^1 es O, el acoplamiento de una quinazolina de la Fórmula XI



en donde Q^1 , Z , L , R^2 , R^3 y Q^2 son como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, con un alcohol de la Fórmula Q^3OH en donde cualquier grupo funcional en Q^3 se protege, si es necesario, a partir de lo cual cualquier grupo protector que esté presente se retira por medios tradicionales; o

(e) para la producción de aquellos compuestos de la Fórmula I en donde R^1 es un grupo hidroxilo, la escisión de un derivado de quinazolina de la Fórmula I en donde R^1 es un grupo (1-6C)alcoxi o arilmetoxi; o

(f) para la producción de aquellos compuestos de la Fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo amino primario o secundario, la escisión del

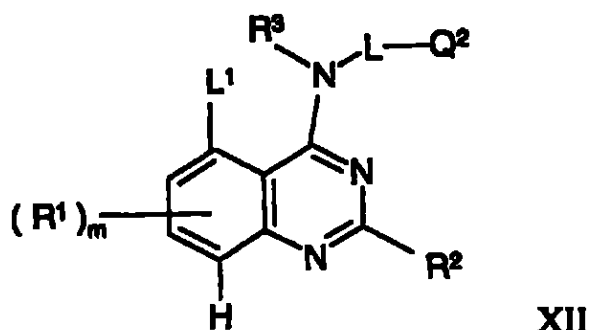
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compuesto correspondiente de fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo amino primario o secundario protegido; o

(g) para la producción de aquellos compuestos de la Fórmula I en donde Q^1 , R ó Q^2 contiene un grupo (1-6C)alcoxi o (1-6C)alcoxi sustituido o un grupo (1-6C)alquilamino o (1-6C)alquilamino sustituido, la alquilación de un derivado de quinazolina de la Fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo hidroxilo o un grupo amino primario o secundario, según sea apropiado; o

(h) para la producción de aquellos compuestos de la Fórmula I en donde Q^1 , R^1 ó Q^2 contiene grupo (1-6C)alcoxi amino-hidroxilo-disustituido, la reacción de un compuesto de la Fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo (1-6C)alcoxi epoxi-sustituido con compuesto heterociclilo o una amina apropiada; o

(i) la reacción de una quinazolina de la Fórmula XII



en donde L^1 es un grupo desplazable y m , R^1 , R^2 , R^3 y Q^2 son como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, con un compuesto de la Fórmula:



en donde Q^1 y Z son como se define en la reivindicación 1 excepto que cualquier grupo funcional se protege, si es necesario, a partir de lo cual cualquier grupo protector que esté presente se retira por medios tradicionales; o

(j) para la producción de aquellos compuestos de la Fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo (1-6C)alcoxi amino-sustituido, la reacción de un compuesto de la Fórmula I en donde Q^1 , R^1 o Q^2 contiene un grupo(1-6C)alcoxi halógeno sustituido con un compuesto heterociclilo o

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una amina apropiada; o

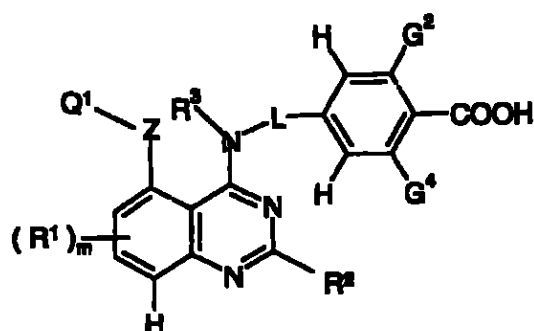
(k) para la producción de aquellos compuestos de la Fórmula I en donde un grupo heterociclilo en R^1 , Q^1 o Q^3 contiene un S- o N-óxido, la oxidación de un anillo N o átomo S en un compuesto de la Fórmula (I); o

(l) para la producción de aquellos compuestos de la Fórmula I en donde Q^2 es un grupo de la fórmula 1a y:

(i) G^3 es un grupo de la fórmula $CON(R^{20})Q^{10}$ en donde R^{20} y Q^{10} son como se define en la reivindicación 1, ó

(ii) G^3 es un grupo de la fórmula COQ^{10} y Q^{10} es un grupo heterociclilo enlazado nitrógeno,

el acoplamiento de la correspondiente quinazolina carboxi sustituida de la Fórmula XIII



XIII

o un derivado reactivo del mismo, con una amina de la Fórmula $NH(R^{20})Q^{10}$ ó $Q^{10}H$, según lo apropiado, en donde R^1 , R^2 , R^3 , R^{20} , Q^1 , Q^{10} , Z , l , m , G^2 y G^4 son como se define arriba en el texto, excepto que cualquier grupo funcional se protege, si es necesario, a partir de lo cual cualquier grupo protector que esté presente se retira por medios tradicionales; o

(m) para la producción de aquellos compuestos de la Fórmula I en donde G^3 en Q^2 es un grupo de la fórmula OQ^{10} en donde Q^{10} es aril(1-6C)alquilo, heteroaril(1-6C)alquilo, o heteroarilo, la reacción de compuesto de fórmula I en donde G^3 en Q^2 es OH con un compuesto de la Fórmula $Q^{10}-L^1$ en donde L^1 es un grupo desplazable, y cualquier grupo funcional en Q^{10} se protege, si es necesario, y, a partir de entonces, cualquier grupo protector que esté presente se retira por medios tradicionales; o

(n) para la producción de aquellos compuestos de la Fórmula I en donde

cualquiera de Q^1 , R^1 ó Q^2 contiene un grupo (2-6C)alcanoilamino, (2-6C)alcanoilamino sustituido, la acilación de un derivado de quinazolina de la Fórmula I en donde Q^1 , R^1 ó Q^2 contiene un grupo amino; o

(o) para la producción de aquellos compuestos de la Fórmula I en donde R^1 , Q^1 ó Q^2 contiene un grupo (1-6C)alquilamino o (1-6C)alquilamino sustituido o un grupo heterociclilo enlazado a nitrógeno, la aminación reductora de un grupo aldehído o cetona en un compuesto de fórmula 1, con un grupo (1-6C)alquilamina, (1-6C)alquilamina sustituidos o un heterociclo que contiene un grupo NH en la presencia de un agente reductor apropiado; o

(p) la conversión de un compuesto de la Fórmula I en otro compuesto de la Fórmula I;

y, cuando se requiere, una sal farmacéuticamente aceptable de un derivado de quinazolina de la Fórmula I, éste puede obtenerse usando un procedimiento tradicional.

23. Una composición farmacéutica que comprende un derivado de quinazolina de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define en la reivindicación 1 en asociación con un diluyente o transportador farmacéuticamente aceptables.

24. Un derivado de quinazolina de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define en la reivindicación 1 para uso en un método de tratamiento del cuerpo humano o animal por terapia.

25. El uso de un derivado de quinazolina de la Fórmula I, o una sal farmacéuticamente aceptable del mismo, como se define en la reivindicación 1 en la manufactura de un medicamento en la prevención o tratamiento de tumores que son sensibles a la inhibición de una o más tirosina cinasas de receptor erbB.

PATENT COOPERATION TREATY

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From the

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:		CODE	DATE	NTD
Nelson, Michael Andrew ASTRAZENECA Global Intellectual Property Meraside, Alderley Park Macclesfield Cheshire, SK10 4TG GRANDE BRETAGNE				
		NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT	13 OCT 2003	
		DATA ENTERED		
		FINAL CHECK		
		Date of mailing (day/month/year) 12/09/2003		
Applicant's or agent's file reference 100527/WO		IMPORTANT NOTIFICATION		
International application No. PCT/GB 02/ 04932	International filing date (day/month/year) 31/10/2002	Priority date (day/month/year) 03/11/2001		
Applicant ASTRAZENECA AB et al.				

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epru d
Fax: (+49-89) 2399-4465

Authorized officer

PITTORRU R
Tel (+49-89) 2399 2828



PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 100527/W0	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 02/ 04932	International filing date (day/month/year) 31/10/2002	Priority date (day/month/year) 03/11/2001
International Patent Classification (IPC) or national classification and IPC C07D239/94		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 19/05/2003	Date of completion of this report 09/09/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer GELLIE B R Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/ GB 02/ 04932

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I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

From the INTERNATIONAL BUREAU

06 JUN 2003

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NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To: ASTRAZENECA Global Intellectual Property Mereside Alderley Park Macclesfield, Cheshire ROYAUME-UNI	CODE	DATE	NTD
	ANKOM 02 JUN 2003		GIPB
	SK10.4TG		
	DATA ENTERED		
FINAL CHECK			

Date of mailing(day/month/year) 15 May 2003 (15.05.03)		IMPORTANT NOTICE	
Applicant's or agent's file reference 100527/WO			
International application No. PCT/GB02/04932	International filing date(day/month/year) 31 October 2002 (31.10.02)	Priority date(day/month/year) 03 November 2001 (03.11.01)	
Applicant ASTRAZENECA AB, et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EG, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 15 May 2003 (15.05.03) under No. 03/040109

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume IA, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Judith Zahra
Facsimile No.(41-22) 740.14.35	Telephone No.(41-22) 338.91.11

PCT REQUEST

Original (for SUBMISSION) - printed on 29.10.2002 05:38:28 PM

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0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	100527/WO
I	Title of invention	QUINAZOLINE DERIVATIVES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	AP: (GH GM KE LS MW ME SD SL SE SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MK MN MW MX ME NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address:	Sodertalje S-151 85 Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+44 1625 230148
II-9	Facsimile No.	+44 1625 510752

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III-1	Applicant and/or Inventor	
III-1-1	This person is:	applicant only
III-1-2	Applicant for	MG
III-1-4	Name	ASTRAZENECA UK LIMITED
III-1-5	Address:	15 Stanhope Gate London, Greater London W1K 1LN United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB
III-2	Applicant and/or Inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	HERNEQUIN, Laurent, Francois, Andre
III-2-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-2-6	State of nationality	FR
III-2-7	State of residence	GB
III-3	Applicant and/or Inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	KETTLE, Jason, Grant
III-3-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-3-6	State of nationality	GB
III-3-7	State of residence	GB
III-4	Applicant and/or Inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	PASS, Martin
III-4-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-4-6	State of nationality	GB
III-4-7	State of residence	GB
III-5	Applicant and/or Inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	BRADBURY, Robert, Hugh
III-5-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-5-6	State of nationality	GB
III-5-7	State of residence	GB

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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	ASTRAZENECA
IV-1-2	Address:	Global Intellectual Property Maraside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV-1-3	Telephone No.	+44 1625 230148
IV-1-4	Facsimile No.	+44 1625 510752
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: CH GM KE LS MW ME SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BE CA CH LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MY NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

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V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	03 November 2001 (03.11.2001)	
VI-1-2	Number	0126433.2	
VI-1-3	Country	GB	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	239	-
IX-3	Claims	35	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	280	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Figure of the drawings which should accompany the abstract		

PCT REQUEST

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IX-20	Language of filing of the international application	English
X-1	Signature of applicant, agent or common representative	M. W. H.
X-1-1	Name	ASTRAZENECA
X-1-2	Name of signatory	AGENT
X-1-3	Capacity	ASTRAZENECA

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT (ANNEX - FEE CALCULATION SHEET)

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100527/WO

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only		
0-1	International Application No.		
0-2	Date stamp of the receiving Office		
0-4	Form - PCT/ROH/01 (Annex) PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)	
0-9	Applicant's or agent's file reference	100527/WO	
2	Applicant	ASTRAZENECA AB, et al.	
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (GBP)
12-1	Transmittal fee T	⇒	55
12-2-1	Search fee S	⇒	592
12-2-2	International search to be carried out by	EP	
12-3	International fee		
	Basic fee (first 30 sheets) b1	278	
12-4	Remaining sheets	250	
12-5	Additional amount (X) b2	6	
12-6	Total additional amount	1,500	
12-7	b1 + b2 = B	1,778	
12-8	Designation fees		
	Number of designations contained in international application	94	
12-9	Number of designation fees payable (maximum 5)	5	
12-10	Amount of designation fee (X)	60	
12-11	Total designation fees D	300	
12-12	PCT-EASY fee reduction R	-86	
12-13	Total international fee (B+D-R) I	⇒	1,992
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒	2,639
12-19	Mode of payment	cheque	
12-20	Deposit account instructions		
	The receiving Office:	United Kingdom Patent Office (RO/GB)	
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓	
12-20-3	Authorization to charge the fee for priority document.	✓	
12-21	Deposit account No.	D02934	
12-22	Date	29 October 2002 (29.10.2002)	

PCT (ANNEX - FEE CALCULATION SHEET)

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100527/NO

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12-23	Name and signature	ASTRAZENECA M. W. W.
-------	--------------------	-------------------------

VALIDATION LOG AND REMARKS

13-2-3	Validation messages Names	Yellow Applicant 1.: City missing
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.

PCT

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100527/WO

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PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

Yellow	Names Applicant 1..City missing
Green?	Contents The international application contains no drawings. Please verify.

Before submitting the International Application, please carefully verify that:

- the information contained on printed Request form is correct;
- Box X of the Request form has been signed;
- all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,
- the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

ABSTRACT

TITLE : QUINAZOLINE DERIVATIVES

The invention concerns quinazoline derivatives of Formula I

(A chemical formula should be inserted here - please see paper copy enclosed)

wherein each of Q1, Q2, Z, R1, R2, R3, L and m have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use for use in the prevention or treatment of tumours which are sensitive to inhibition of erbB receptor tyrosine kinases.

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**POWER OF ATTORNEY CONCERNING
A GIVEN INTERNATIONAL APPLICATION
PATENT CO-OPERATION TREATY**

The undersigned applicants ASTRAZENECA AB of S-151, 85 Sodertalje, Sweden,
ASTRAZENECA UK LIMITED of 15 Stanhope Gate, London, W1Y 6LN, United Kingdom,
Laurent Francois Andre HENNEQUIN, Jason Grant KETTLE, Martin PASS and Robert
Hugh BRADBURY hereby appoint:

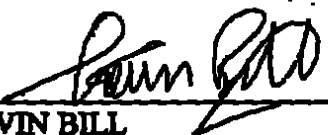
KEVIN BILL	NEIL GODFREY ALASDAIR PHILLIPS
TRACEY BRYANT	LAURENCE DAVID SCOTT GAINEY
PAUL MILLINGTON DENERLEY	BRIAN STEELE TAIT
ALLEN FRANK GILES	JOHN RICHARD MACK
IAN GORDON BERRY	MICHAEL ANDREW NELSON
ANDREW FARQUHARSON	RACHEL MARIA TINSLEY
TRACY ANNE BURNS	FRANCIS JOHN TIERNEY
RICHARD SUMMERSELL	ANNA GRIFFITHS-JOHNSON

All of : Global Intellectual Property
AstraZeneca
Mercedes
Alderley Park, Macclesfield
Cheshire, SK10 4TG,
United Kingdom

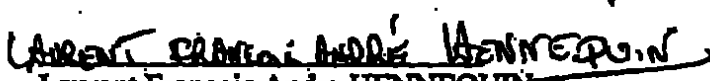
as Agent to act on their behalf before the competent International Authorities in connection
with the International Application concerning:

QUINAZOLINE DERIVATIVES

Case No.100527/WO, filed with the United Kingdom Patent Office and to make or receive
payment on their behalf.

622
622
KEVIN BILL

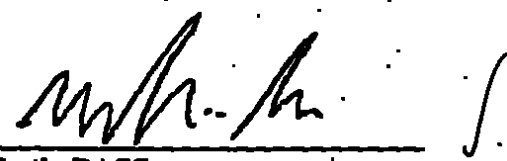
Of: Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom
AUTHORISED OFFICER FOR
ASTRAZENECA AB & ASTRAZENECA UK LIMITED
Date: 4th October 2002


Laurent Francois Andre HENNEQUIN

Of: Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom
Date: 14th of October 2002


Jason Grant KETTLE

Of: Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom
Date: 16 October 2002


Martin PASS

Of: Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom
Date: 16th Oct 2002


Robert Hugh BRADBURY

Of: Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom
Date: 11 October 2002

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only		
Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 100527/WO
International application No. PCT/GB02/04932	International filing date (day/month/year) 31 October 2002 (31.10.2002)	(Earliest) Priority date (day/month/year) 03 November 2001 (03.11.2001)
Title of invention QUINAZOLINE DERIVATIVES AS ANTITUMOR AGENTS		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) AstraZeneca AB S-151 85 Södertälje Sweden		Telephone No. +44 1625 5130148
		Facsimile No. +48 8 553 28820
		Teleprinter No.
		Applicant's registration No. with the Office
State (that is, country) of nationality: SE		State (that is, country) of residence: SE
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ASTRAZENECA UK LIMITED 15 Stanhope Gate London W1Y 1KN United Kingdom		
State (that is, country) of nationality: GB		State (that is, country) of residence: GB
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) HENNEQUIN, Laurent, Francois Andre Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom		
State (that is, country) of nationality: FR		State (that is, country) of residence: GB
☒ Further applicants are indicated on a continuation sheet.		

M
2624

Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet should not be included in the demand.*Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KETTLE, Jason Grant
Alderley Park
Macclesfield
Cheshire SK10 4TG
United Kingdom

State *(that is, country)* of nationality:
GBState *(that is, country)* of residence:
GBName and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PASS, Martin
Alderley Park
Macclesfield
Cheshire SK10 4TG
United Kingdom

State *(that is, country)* of nationality:
GBState *(that is, country)* of residence:
GBName and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BRADBURY, Robert Hugh
Alderley Park
Macclesfield
Cheshire SK10 4TG
United Kingdom

State *(that is, country)* of nationality:
GBState *(that is, country)* of residence:
GBName and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*State *(that is, country)* of nationality:State *(that is, country)* of residence:☐

Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)NELSON, Michael Andrew
ASTRAZENECA
Global Intellectual Property
Mersey, Alderley Park
Macclesfield,
Cheshire, SK10 4TG
United Kingdom

Telephone No.

+44 1625 514113

Facsimile No.

+46 8 553 28820

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed
☐ as amended under Article 34the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34the drawings ☐ as originally filed
☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

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Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|---|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☐ copy of general power of attorney;
reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

.....
NELSON, Michael Andrew et al
Global Intellectual Property, Patents, AstraZeneca AB

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due
to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months
from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been
informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of
Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival
is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

CHAPTER I

627

International application No. PCT/GB02/04932 Applicant's or agent's file reference 100527/WO Applicant AstraZeneca AB et al CALCULATION OF PRESCRIBED FEES 1. Preliminary examination fee EURO 1530.00 P 2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>) EURO 159.00 H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box EURO 1689.00 TOTAL	For International Preliminary Examining Authority use only Date stamp of the IPEA								
MODE OF PAYMENT <table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (<i>This mode of payment may not be available at all IPEAs</i>) <table style="width: 100%;"> <tr> <td style="width: 50%;"> ☒ Authorization to charge the total fees indicated above. ☒ (<i>This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. </td> <td style="width: 50%;"> IPEA/ <u>EPO</u> Deposit Account No.: <u>2810 0023</u> Date: _____ Name: <u>Frank Loftus</u> Signature: _____ </td> </tr> </table>		☒ Authorization to charge the total fees indicated above. ☒ (<i>This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>EPO</u> Deposit Account No.: <u>2810 0023</u> Date: _____ Name: <u>Frank Loftus</u> Signature: _____						
☒ Authorization to charge the total fees indicated above. ☒ (<i>This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>EPO</u> Deposit Account No.: <u>2810 0023</u> Date: _____ Name: <u>Frank Loftus</u> Signature: _____								

Brigard & Castro

BOGOTA - COLOMBIA

PODER

POWER OF ATTORNEY

Yo (nosotros)

I (We) ASTRAZENECA AB

domiciliado(s) en

domiciled in SE-151-3odertalje, Sweden

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

Hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages: claims or observations on patent applications, models, industrial designs and utility models; In the exercise of preventive measures: and in other actions or similar proceedings.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades legales necesarias.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S. domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

This power includes the faculty to ratify or confirm, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S. domiciled in Carrera 7 No. 16-56 Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial or extra-judicial attorneys.

Otorgado y firmado en

Granted and signed in

hoy de de 200_

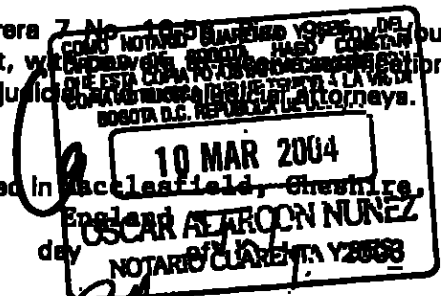
this day

Firma

Signature

Nombre
Cargo

Name
Title



110816

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy _____ de _____ de _____
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el
anterior documento, debidamente juramentado declaró
y dijo que él es

de

Sociedad legalmente constituida para un período de
duración que aún no ha terminado; que el declarante
está autorizado por dicha compañía para conferir este
poder; que el sello estampado por él al pie de tal poder,
en nombre y representación de la expresada compañía,
es el sello oficial de ella; y que el objeto para el cual se
confiere este instrumento está comprendido dentro del
de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

Estado de _____
con fecha _____

que quien confiere el presente poder es su
representante.



Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

py _____ de _____ de _____, compareció(eron)
nte mí

a quien (es) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que precede y
quien(es) declara(n) que otorgan el mismo para los
fines y propósitos que en él se expresan.

Notario Público (sello)

LEGALIZACIÓN POR APOSTILLA ES REQUERIDA.

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of _____
personally appeared before me

KEVIN BILLY
to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the

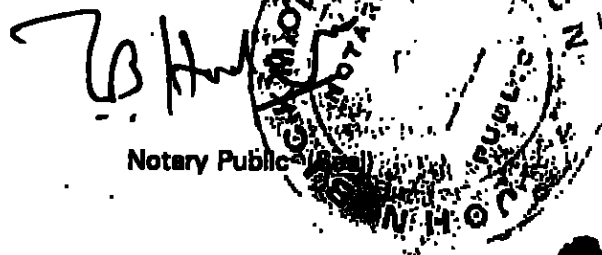
ATTORNEY
of ATRAZNECA AB

Which is legally constituted for a term not yet expired,
that deponent is authorized by said Company to confer
-this Power of Attorney: that the seal affixed hereunto
by the deponent in the name and on behalf of said
Corporation is the corporate seal thereof; and that the
purpose for which this instrument is granted is
included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen
the documents that prove the existence of the
company.

State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of
attorney is its Representative.

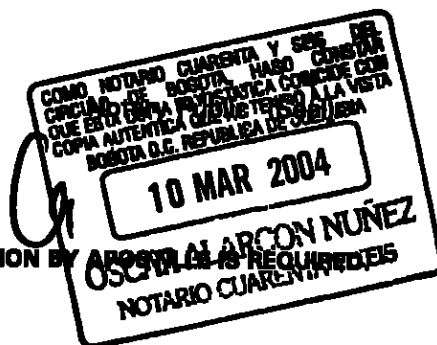


Notario Público (sello)

**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this _____ day of _____ of _____
personally appeared before me

who la(ara) known to me and who I attest executed
the foregoing document and he (they) declared he
(they) grant(s) the document for the uses and purposes
therein expressed.



LEGALIZATION BY APOSTILLA IS REQUIRED

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APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by J B Hodgson
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

Certified/Attesté

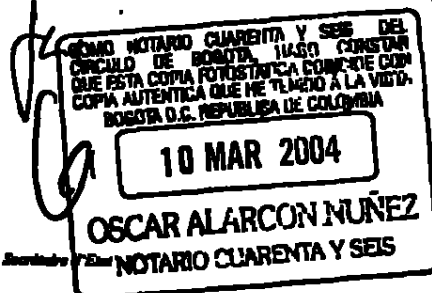
6. the/le 17 February 2004

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No G348987

9. Stamp:
timbre

10. Signature: J. Ireland



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

628
630

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

PATENTE DE INVENCION

MODELO DE UTILIDAD

USUARIO RADICADOR

Indicación de que se solicita la concesión de una patente
Datos de identificación del solicitante de la persona que se presenta la solicitud
Descripción de la invención
Dib. de esta parte pertinente
Comprobante de Pago de las tasas establecidas

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COMPLETA ()

INCOMPLETA () ()

DISEÑO INDUSTRIAL ()

Indicación de que se solicita el registro de Diseño Industrial
Datos de identificación del solicitante o de la persona que presenta la solicitud
Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño
Comprobante de pago de las tasas establecidas

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COMPLETA ()

INCOMPLETA () ()

ESQUEMA DE TRAZADO ()

Indicación de que solicita el registro de un Esquema de trazado
Datos de identificación del solicitante o de la persona que presenta la solicitud
Representación gráfica del esquema de trazado
Comprobante de pago de las tasas establecidas

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COMPLETA ()

INCOMPLETA () ()

Firma Responsable

Fecha

SUPERINDUSTRIA Y COMERCIO
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Fecha (AMD) 2004-06-02 17:27:56
Tramite 011 PCT-PATENT 379 FASE MACI 411 PRESENTAR
Dependencia 2020 DIVISION DE NUEVAS CREACIONES